IMPACT OF PERIOPERATIVE ENTERAL SYNBIOTICS IN SURGERY FOR CHRONIC PANCREATITIS:

A SINGLE BLIND PROSPECTIVE RANDOMIZED CONTROL TRIAL

Dissertation Submitted to

THE TAMILNADU DR. M.G.R. MEDICAL UNIVERSITY

in partial fulfillment of the regulations
for the award of the degree of

M.Ch (SURGICAL GASTROENTEROLOGY & PROCTOLOGY)
BRANCH – VI

INSTITUTE OF SURGICAL GASTROENTEROLOGY & LIVER TRANSPLANTATION

GOVT. STANLEY MEDICAL COLLEGE & HOSPITAL
THE TAMIL NADU DR. M.G.R. MEDICAL UNIVERSITY
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AUGUST 2014

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Dr. AL. MEENAKSHI SUNDARAM, M.D., D.A.,
DEAN
Govt. Stanley Medical College
& Hospital,
Chennai-600 001.

Prof.G.MANOHARAN,M.S.,M.Ch.,
Professor & Head
Institute of Surgical Gastroenterology
& Liver Transplantation
Govt. Stanley Medical College
Chennai-600 001.

DECLARATION

I, **Dr. ASHWIN RAMMOHAN,** solemnly declare that the dissertation entitled, **"IMPACT OF PERIOPERATIVE ENTERAL SYNBIOTICS IN SURGERY FOR CHRONIC PANCREATITIS:** ***A SINGLE BLIND PROSPECTIVE RANDOMIZED CONTROL TRIAL*****"** is a bonafide work done by me at Govt. Stanley Medical College & Hospital during under the guidance and supervision of **Prof. G.MANOHARAN, M.S., M.Ch,** Professor and Head, Institute of Surgical Gastroenterology & Liver Transplantation, Stanley Medical College, Chennai-600 001.

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Name & Signature of the Guide:

Prof. G.Manoharan M.S., M.Ch.,

Name & Signature of Head of the Department:

Prof. G.Manoharan M.S., M.Ch.,

Name & Signature of the Dean:

Dr.AL.Meenakshi Sundaram,M.D., D.A,

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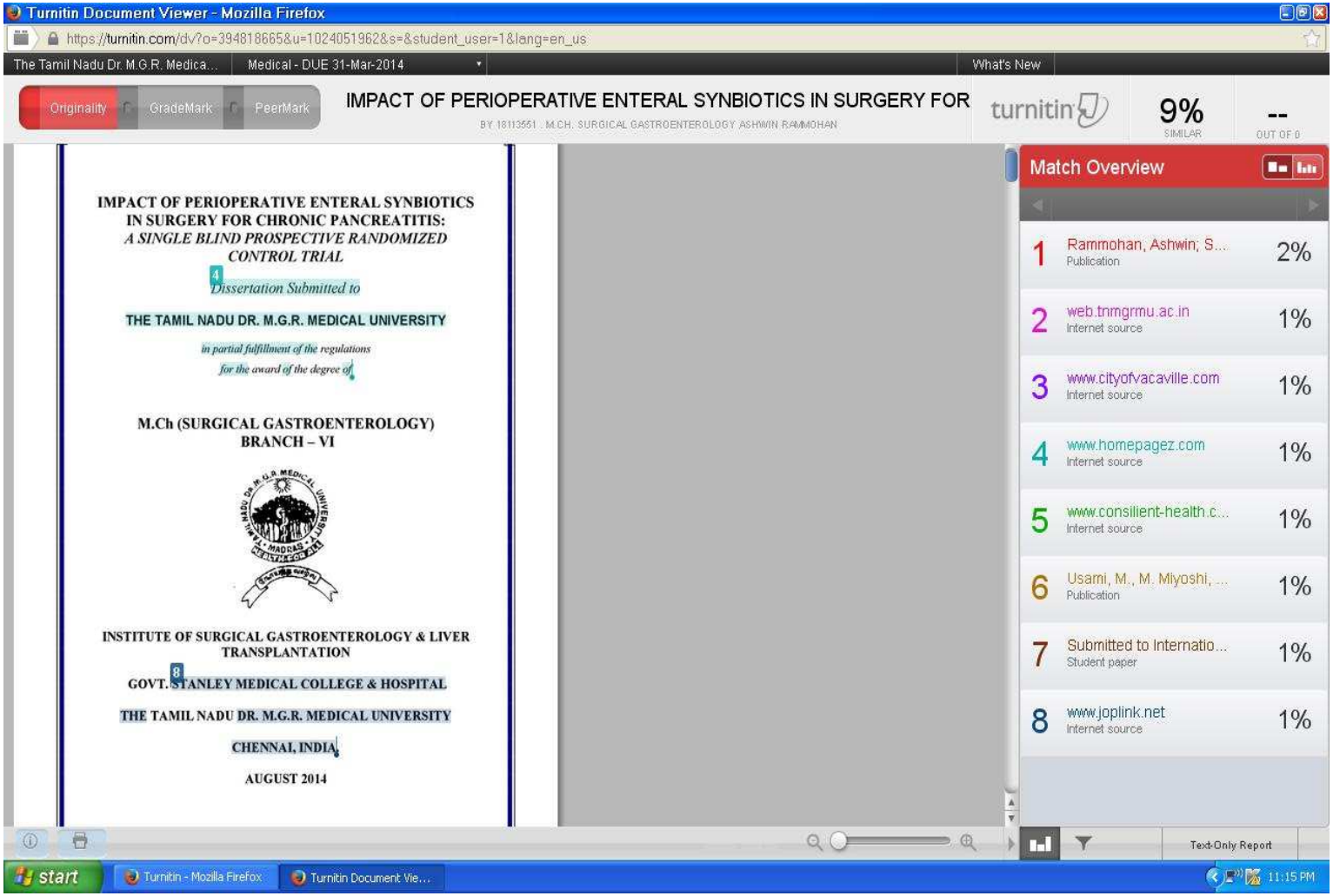
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INTRODUCTION

INTRODUCTION

Despite immense advances in intensive care medicine, surgical technique, and hygiene; nosocomial infections still represent a major clinical problem in modern-day surgery.[1] According to a survey of 3,147 patients admitted to a surgical intensive care unit, infection was identified in 37% of the patients causing 24% mortality.[2] Another recent study has shown that in patients with post surgical sepsis, 85% had an intra-abdominal source.[3] Male gender, advanced age, presence of comorbidities, inadequate nutritional status, complications of operations, shock, multisystem organ failure, high APACHE II-score, emergency procedures, and multiple procedures were among the most common risk factors for hospital acquire infections in surgical patients.[2,3].

Pancreatic surgery is fraught with infectious complications. Inspite of standardized techniques atleast 10% of patients develop intra-abdominal abscesses while another 10% experience wound infections.[4] These numbers exponentially increase, if other complications such as pancreatic leak or delayed gastric emptying occur.[4, 5]

Even in the highest-volume centers, pancreatic resections are associated with a high overall morbidity, in the range of 35% to 60%.[4,5] These figures remain constant even in the large volume centres across continents.[6,7] In a recent review, infections occurred in nearly one-third

of patients. In patients undergoing proximal or distal pancreatic resections, infections occurred in nearly 30% of cases and accounted for a 40% escalation in the total cost of the procedure along with a increased duration of hospital stay.[6] Pancreatic fistula with a collection / abscess (28%), followed by wound infection (24%) accounted for the majority of infections.[4,5,6] Other causes included pneumonia (17%), abscess (15%), urinary tract infection (10%), and sepsis (6%). Most of them started off with one infection and progressed to multiple infections. These are responsible for a significant financial, economic and emotional burden on patients, doctors, and healthcare system alike.[3,4,6,7]

These infections occur despite a strict adherence to infection control regulations, standardized surgical techniques, refinements in perioperative care, use of aggressive and appropriate evidence based perioperative antibiotic prophylaxis and potent antibiotics. [3,4,6,7] This emphasizes the necessity to find better process improvements to decrease infectious complications, a few of which include reevaluating the effectiveness of antimicrobial prophylaxis regimens and regular auditing.

Post-surgical morbidity due to septic manifestations is only partly attributed to the surgeon and the surgical technique. Increasing evidence suggests instead that it is the patient's ability to resist disease/immune defense and especially supportive measures during and around the treatment, such as mechanical ventilation, use of implants, drains and intravascular lines, but also choice of content and routes to provide

nutrition, blood transfusions, choice of anesthesia and prescription of drugs, also antibiotics and immunosuppressives, that are the largest contributors to the development of septic manifestations.

Mechanical ventilation in association with management of emergencies and surgical procedures has in recent years received increasing attention as a major contributor for not only chest-infections, but also for other general and localized septic manifestations in the body.[8] This treatment is responsible for, not only a disproportional amount of resources used, but also for the unacceptably high morbidity and mortality associated with the treatment, especially in elderly people.[6] A main contributor to intensive care unit (ICU)-associated sepsis is also artificial nutrition, both enteral and parenteral; catheter-related sepsis is reported to occur in about 25% of patients fed via intravenous feeding-tubes.[3,7]

Numerous drugs used in the ICUs including antibiotics are known to derange the immune functions, impair macrophage functions, bactericidal efficacy as well as production and secretion of cytokines. Other common perioperative practices like use of artificial feeding regimens, preoperative antibiotics, and mechanical bowel preparation will also contribute to increased rates of treatment-associated infections

The intestinal lining is the first line of defense against bacteria, it isolates the systemic circulation from the bacteria. [8,9] The intestinal epithelium consists of a single layer of columnar cells starting at the

gastroesophageal junction and extending to the squamous epithelium of the anal canal. This physical barrier is selectively permeable and capable of preventing transmigration of pathologic luminal substances from the external environment, that is, the lumen, to the internal environment.[8,9] The basal and apical portions of the cells are closely bound to one another with filaments, to maintain normal polarity and tight junctions.[8,9,10,11] Cell turnover occurs in a systematic fashion approximately every 5 to 7 days under the control of various growth factors, including epidermal growth factor, intestinal trefoil factor etc. [8,9,10,11]

This mucosal epithelial lining is covered by microproteins in the form of mucin, which coats the surface to create a physical barrier against the bacteria. Mucin contains high concentrations of antibacterial molecules such as defensins and others like lactoferrin, lysozymes, and sPLA2.[10,11,12,13] sPLA2 destroys the integrity of the bacterial cell wall, whereas lactoferrin impairs the ability of bacteria to adhere to epithelial cells. [8,9,10,11,12] Bacterial invasion occurs under conditions of surgical stress along with alterations in normal oral intake and reductions in the mucin layer leading onto an impairment of the antimicrobial peptides in the mucin layer, and increased mucosal permeability weakening this intrinsic defense mechanism.[13,14,15,16,17] This disruption of the gut barrier can result in systemic inflammation and septic complications. [12,13] Disruption of gut barrier function and intestinal microbial imbalance can

result in systemic inflammation and ultimately induce septic complications after surgery.[6,7,12]

The true size and diversity of the human microbiota is largely unfathomed.[14,15] The application of modern technologies—genomics, metagenomics, and metabolomics—to the study of the colonic microbiota has the potential to expose the true diversity and metabolic profile of the microbiota and the reveal the real extent of changes which occur in a diseased state.[16,17,18,19,20,21] Techniques based on 16S rDNA sequences have revealed that the diversity of the human microbiota is far greater than previously assumed and that most bacterial sequences are unculturable sequences and novel bacteria.[18,19] Metagenomics indicate that the human gut houses somewhere to the order of 30,000 to 40,000 different microorganisms, and their physiological roles organisms are yet to be discovered.[16,17]

The human bowel houses about 10^{14} viable microorganisms, which constitute 95% of the cells in our bodies, the size of their population exceeds the total number of somatic and germ cells in our body.[12,16] Most of the bacteria are located in the colon. [12,17] The so-called indigenous gut microbiota has several important functions which include prevention of colonization by pathogenic organisms, modulation of local and systemic immunity, feeding of enterocytes, and maintenance of intestinal motility and mucus secretion to just name a few. [11,12,13,14,16,17]

The gut microbiota or microflora has a crucial role in human health and disease. The GIT is comprised of the entire digestive system from the stomach to the anus. The colon is the organ which is the preferred site for bacterial colonization. The GIT is also rich in many molecules which can be used as nutrients by microbes. The mucosa of the gastrointestinal tract is continuously exposed to an environment that is rich in foreign substances, such as food particles and antigens of microbial origin.[2,4,8] Particular changes in the intestinal ecosystem might contribute to the development of certain illness. There is therefore a need for an exhaustive review on the functions of the gut microbiota, occurrence of gut dysbiosis (alteration or imbalance of the microflora), how these intestinal bacteria trigger development of disease once the normal flora of a healthy individual is imbalanced, exploiting this intricate and interwoven ecosystem for understanding human health, development of biotherapeutics, and future perspectives.[3,8,9,10]

The composition of this gut bionome is not the same across the length of the gut, it demonstrates variation along its diameter, with certain bacteria tending to be adherent to the mucosal surface while others predominate in the lumen. [18,19,20] The composition of the microbiota is also influenced by age, diet, socioeconomic conditions and the use of antibiotics. These bacteria help to the shape individual human physiology by influencing the expression of genes critical to the proper development of intestines and their function, including nutrient absorption and

metabolism, metabolism of toxins, gut maturation, and angiogenesis.[14,16,17,18]

The process by which intraluminal bacteria transgress the intestinal mucosa to reach the local lymph nodes is called bacterial translocation. This translocation by potentially pathogenic bacteria has been associated with an increased incidence of postoperative sepsis. Bacterial translocation after pancreatic surgery has been reported to occur in 20% of mesenteric lymph nodes, and these patients commonly experience infections and complications.[12,13]

Patients undergoing surgery have several risk factors for disturbance of the intestinal microflora, resulting in translocation from pathogenic bacteria into mesenteric lymph nodes, blood, and other organs. [14,16,17,18] Decreased postoperative intestinal motility, jaundice, antibiotics usage, loss of mucosal barrier function due to malnutrition, manipulation of the bowel, parenteral nutrition, suppression of the immune system by blood products and operative trauma are all factors which promote this translocation.[12,13,14,16,17]

A certain degree of bacterial translocation is physiological and has been shown to occur after sham operations. [14] Severe bacterial overgrowth and subsequent translocation results in bacterial infections or even sepsis. [13,14,16] The majority of these observed infections are caused by bacteria from the gut, especially *Enterococci* and *Escherichia coli,* which

translocate into mesenteric lymph nodes or into the blood. In study analyzing the microbiology of subphrenic abscesses, aerobic bacteria were cultivated in 13%, anaerobic bacteria in 21%, and a mixed flora in 65%, with clear predominance of Escherichia coli, Enterococci, Staphylococcus aureus, and Bacteroides fragilis.[4,13,17,18,19,20] Bacterial smears in patients with postoperative peritonitis in 355 patients showed E. coli in 51%, Enterococci in 30% and B. fragilis in 25%.[4]

There are three general methods by which the intestinal microflora can be altered: administration of antibiotics, prebiotics (i.e., dietary components that promote the growth and metabolic activity of beneficial bacteria), probiotics (i.e., beneficial bacteria), or fecal transplant (bacteriotherapy). Combination of these methods is also possible (synbiotics). Interest in these approaches has extended well beyond the clinical sciences since a role for intestinal microbes in health and disease has been recognized in alternative and complementary forms of medicine for many years

Fecal microbiota transplantation (FMT) is the process of transplantation of fecal bacteria from a healthy individual into a recipient. It has been proven to be a highly effective treatment for patients suffering from *C.Difficile* induced pseudomembraneous colitis.[18,19] Previous terms for the procedure include fecal bacteriotherapy, fecal transfusion, fecal transplant, stool transplant, fecal enema and human probiotic infusion (HPI). The procedure involves the complete restoration of the entire fecal

microbiota, by introducing healthy bacterial flora through infusion of stool, e.g. by enema, obtained from a healthy human donor.[19] Infusion of feces from healthy donors was demonstrated in a randomized, controlled trial to be highly effective in treating recurrent *C. difficile*, and more effective than vancomycin alone.[21] It can also be used to treat other conditions, including colitis, constipation and irritable bowel syndrome and some neurological conditions. A modified form of fecal bacteriotherapy (Autologous Restoration of Gastrointestinal Flora - ARGF) which involves an autologous fecal sample, provided by the patient before medical treatment, stored in a refrigerator.[16,18] Should the patient subsequently develop *C. difficile*, the sample is extracted with saline and filtered. The filtrate is freeze-dried and the resulting solid enclosed in enteric-coated capsules.

It was once considered to be "last resort therapy" due to its unusual nature and 'invasiveness' compared with antibiotics. Due to the psychological barrier along with a perceived potential risk of infection transmission, the recent position statement by specialists in infectious diseases and other societies is divided as to its indications in mainstream gastroenterology. Probiotics are able to partially provide the beneficial microbiological milieu, as offered by FMT. [18,19,20]

Probiotics were first described by Metchnikoff in 1908 based on his observations on the longevity of individuals who lived in a certain part of Bulgaria and which he attributed to their ingestion, on a regular basis,

of a fermented milk product. Probiotics are defined by the Food and Agriculture Organization of the United Nations and the World Health Organization (WHO) as live microorganisms that, when administered in adequate amounts, confer a health benefit on the host.[22] Tremendous interest has developed in ways the ecosystem of the gut may be altered, not only to decrease pathogenic numbers but also to promote overall health. Many different foods and supplements that contain microbes—namely, species of bacteria or yeasts—have been used.[22,23] These products are widely known as probiotics, a hybrid word created by combining the Latin *pro-* ("for") with the Greek adjective *-biotic* ("life"). [22] Probiotic is a preparation or product containing a defined single or mixed culture of live microbes that, when ingested in sufficient numbers, will exert beneficial effects on health beyond basic nutrition by altering the gastrointestinal microbiota. [22]

For a food or supplement to be considered as a probiotic, it must meet several criteria. It must contain live organisms capable of colonizing the gastrointestinal tract, implying these organisms need to be acid and bile tolerant. It should improve the health and well-being of the host. They should be generally recognized as safe (GRAS) and non pathogenic. Host-specific strains of organisms should be used; humans should receive strains specific to humans and not of animals.[22]

Thirty to forty species account for 99% of the bacteria present in the human gut and these species are selected to be used therapeutically.

The two most common genera of bacteria used as probiotics are *Bifidobacterium* (e.g., *Bifidobacterium bifidus*) and *Lactobacillus* (e.g., *Lactobacillus reuteri).* Strains of *Streptococcus* and Enterobacteriaceae are less commonly included. *Saccharomyces boulardii*, a probiotic yeast, has been found to have a wide array of benefits and is gaining popularity. Products may contain just one species, or they may contain a mixture of different organisms.[22,23,24]

Probiotics differ in their ability to resist gastric acid and bile acids, colonize the intestinal tract, and influence cytokines secreted by intestinal epithelial cells.[22,23] Thus, not all probiotics are alike; as a result, benefits observed clinically with one species or with a combination of species are not necessarily generalizable to another. Although yogurt is commonly recommended as a source of probiotics, not all of the live cultures contained in yogurt survive well in an acidic environment nor do they colonize the microbiota efficiently.

The science of probiotics is imperfect, with many of its lacunae being scrutinized carefully by investigators world over. In general, demonstrating the colonization of the supplemented probiotic microorganisms has been the primary aim of most studies in healthy individuals. In most cases, a transient colonization of the probiotic microorganisms has been observed. It is still questionable, however, whether probiotic strains would need to colonise in order to be effective

or whether transient presence would also suffice to exert health-beneficial effects.[26]

Administration of a given probiotic strain will result in the temporary increase of that strain the GI tract, but may also change the overall composition of the intestinal microbiota. Which probiotic microorganisms are able to influence the relative abundance of which specific intestinal microorganisms are questions that are currently under study. It is also imperative to realize that a change in composition or diversity of the intestinal microbiota by probiotic intervention is not a health benefit by itself.[24,27] The effects of probiotics on the intestinal microbiota composition in healthy individuals are even more difficult to interpret. Studies do provide information on the effects of probiotics on the intestinal microbiota without a potential bias caused by disease effects. However, this does not imply that in a diseased situation these probiotic products will have the same influence on the intestinal microbiota.

Probiotic studies performed in humans have almost exclusively examined the effect of probiotic administration on the composition of the faecal microbiota, whereas other niches of the GI tract have hardly been studied thus far. This means that there is still a major gap in knowledge on the influence of probiotic microorganisms on the intestinal microbiota.[26,27,28] There is a lack of standardised methods for the study of the intestinal microbiota (e.g. sample collection, sample storage and

analysis methods), which makes it almost impossible to directly compare findings from different groups. Apart from the large variety of probiotic species and strains, different dosages of probiotic; the diverse populations of interest can be relatively heterogeneous since health and disease are not always well defined. All of this, in combination with the fact that the intestinal microbiota composition is diverse and maybe even unique for each individual, makes it problematic to observe general changes in microbiota composition as result of probiotic intervention.[29]

Different strains differ with regard to their ability to colonise and proliferate in the GI tract. Approximately 1-10% of L. acidophilus ingested in fermented product were found to survive until the ileum in several human studies using intestinal intubation techniques.[19,20,27,29] To be effective probiotic cultures must be able to withstand processing conditions, retain their probiotic properties after processing and survive in sufficient numbers in the product during shelf-life storage. The stability of a probiotic is linked to various factors, including genus, species, strain biotype and, above all, the formulation storage conditions.[26,30,31]

The faecal recovery of bifidobacteria and lactobacilli in healthy subjects exhibited a dose response relationship. A 10-fold increase of ingested bacteria caused the average number of recovered viable strain to increase by a factor of 20.[32] Hence the higher the ingested dose, the greater the number of subjects positive for viable bacteria. The suggested minimum viable number is 10^6 CFU/ml or gram, with a recommended

dose of 10^8 CFU/g to compensate for reduction through passage through the gut. It is accepted that at the point of consumption probiotic products should have a minimum concentration of >1 x 10^6 CFU/ml or gram and that a total of some 10^8 to 10^9 probiotic microorganisms should be consumed daily if therapeutic effects are to be realised.[18,19,22,24,25,32]

The fundamental mechanisms of action of probiotics, include, blockade of toxin receptor sites, inhibition of the growth of pathogenic microbes, inhibition of receptor site attachment by pathogens, engagement in cross-talk with other flora thereby enhancing resistance to colonization, enhancement of tight junction bonding and prevention of impaired barrier function, production of cytochrome P-450–like enzymes and facilitation of detoxification, exertion of trophic effects by influencing transport pathways and the production of energy and protein, as well as by releasing enzymes that facilitate the maturation of enterocytes.[25,26,27,28,29,30,31] They also produce B vitamins and vitamin K. Probiotics interact with the immune system and lead to an alteration in secretory immunoglobulin A levels, decrease the inflammatory effects of natural killer cells, and trapping helper T cells in mesenteric lymph nodes to decrease the inflammatory response.[30,31,32,33,34]

These organisms create a physiologically challenging environment (low pH, production of toxic byproducts), by leading to competitive consumption of nutrients, reduction of concentrations of oncogenic enzymes in the gut and by direct DNA signaling.[35,36]

Even dead probiotic organisms can exert an influence on certain aspects of gut physiology; a phenomenon referred to as the probiotic paradox.[37] Secreted proteins and DNA of one probiotic preparation blocked cytokine activation and prevented apoptosis of epithelial cells. The effects depended upon the specific DNA from the different bacterial species that were components of the preparation, and not on the live probiotic itself. Non-methylated DNA from randomly selected *E. coli* strains suppressed experimental colitis in several animal models.[24,26] These therapeutic effects are mediated through toll-like receptor 9 and with induction of type 1 interferons alpha/beta.[27] Defined molecular weight proteins from other probiotic species, including Lactobacillus *GG*, can also inhibit proinflammatory signaling and inflammatory cytokine-induced apoptosis in colonic epithelial cells through an epidermal growth factor receptor (EGFR)-dependent mechanism, while secreted products from a variety of species can inhibit cytokine production.[23,27]

Direct effects include prevention of bacterial overgrowth by secretion of antimicrobial bacteriocines and competitive growth, induction of colonization resistance against pathogenic bacteria by competitive blocking of bacterial adhesion and invasion of epithelial cells, upregulation of intestinal mucus production, and secretion of antimicrobial peptides like beta-defensin 2.[38,39,40] Furthermore, they help in maintaining epithelial integrity through feeding of enterocytes, production of omega-3-fatty acids, inhibition of pathogenic-induced

alterations of epithelial permeability and regulation of enterocyte gene expression.[39,40,41]

Indirectly, some strains are able to specifically stimulate the innate and systemic immune system. [41,42] Probiotics have been shown to modulate the human dendritic cell phenotype and function, to reduce pro-inflammatory cytokines and to induce anti-inflammatory cytokines like IL-10, to stimulate nonspecific resistance to microbial pathogens by activation of macrophages and to increase systemic and mucosal IgA responses.[37,39,40] The relationship between the host's immune system and nonpathogenic constituents of the microbiota is important in protecting the host from colonization by pathogenic species.[42]

The gut bacteria are known to produce a large number of vitamins like the B group of vitamins, synthesize amino acids, and carry out biotransformation of the bile. Biotransformation of bile by microbial enzymes is important for the metabolism of glucose and cholesterol. [33,34,36] Importantly, the microbiome provides the much needed biochemical pathways for the fermentation of nondigestible substrates like fibers and endogenous mucus. Fermentation or metabolism of these nondigestible substrates lead to the growth of these microbes and the production of short chain fatty acids and gases. [33,34]

The major short-chain fatty acids produced are acetate, propionate, and butyrate. Other bacterial end products include lactate, ethanol,

succinate, formate, valerate, caproate, isobutyrate, 2-methyl-butyrate, and isovalerate.[33,36,37] Bacterial fermentation takes place in the cecum and colon, where the short-chain fatty acids are absorbed, stimulating the absorption of salts and water. These short-chain fatty acids have a protective effect on the intestinal epithelium. [33,39,42] The colonic bacteria prefer butyrate as the sole source of energy, and most of it is completely metabolized. The principal short chain fatty acid produced in the colon is acetate, and it serves as a substrate for biosynthesis of cholesterol. Thus, the gut microbiota performs various metabolic acitivities which are essential for the host's metabolism

Prebiotics are nondigestable food constituents that selectively alter growth or activity of one or a limited number of bacterial species in the colon in a manner that potentially improves and promotes the health of the host.[22] Prebiotics reach the colon untouched and serve as colonic food that will be converted by probiotics to important nutrients.[22,24,26,27] They are selectively fermented ingredients that stimulate specific changes in the colonic microbiota which benefit the health of the host.[30,31,32]

While probiotics introduce exogenous bacteria into the human colon, prebiotics stimulate the preferential growth of a limited number of health-promoting species already residing in the colon, especially lactobacilli and bifidobacteria.[38,40] The prototypical prebiotics are the oligosaccharides in human breast milk which facilitate the preferential growth of bifidobacteria and lactobacilli, in the colon, among exclusively

breast-fed neonates; this phenomenon accounts for the immunologic and other benefits that accrue to breast-fed infants.[39,40,41]

The notable prebiotics are the inulin-type fructans, which are linked by β (2–1) bonds that limit their digestion by upper intestinal enzymes, and fructo-oligosaccharides.[29,30,32] They are present in significant amounts in many edible fruits and vegetables, including wheat, onion, chicory, garlic, leeks, artichokes, and bananas. Inulin and oligofructose stimulate the growth of bifidobacteria at the expense of *Bacteroides, Clostridium,* and coliform bacteria.[31,33,34] Chicory fructans have also been shown to enhance the absorption and balance of dietary calcium.[34,35]

Other oligosaccharides, such as xylose, maltose, and mannose, also show promise as prebiotics. Because of their chemical structure, prebiotics are not absorbed in the small intestine but are fermented, in the colon, by endogenous bacteria to energy and metabolic substrates, with lactic and short-chain carboxylic acids as end products of the fermentation.[33,34,41,42]

Used in combination, probiotics and prebiotics are called synbiotics.[41] They are designed to have synergistic or additive effects benefiting the host. The thinking is that consuming both at once, instead of just the probiotic alone, may enhance microbe survival during transit

through the upper gastrointestinal tract and lead to greater positive effects on the beneficial microbes already established in the intestines.[41,42,43]

Synbiotics have demonstrated beneficial effects with respect to the function of innate immunity, intestinal barrier function, and increased resistance to disease. The gut mucosa and microbiota are intimately linked in the maintenance of a functional interface between the host and the external environment.[6,39,40]

Synbiotics have synergistic effects in enhancing immunity and facilitating intestinal barrier function. The term "defense by diversity" was coined in 1999 to reflect the nature of synbiotic treatment.[19] A recent review suggests that multispecies probiotics may be superior to single-species probiotics in reducing antibiotic-associated diarrhea, preventing infections, and reducing pathogenic colonization. [28]

Synbiotics have been found to decrease levels of proinflammatory cytokines, and hence found to be effective in improving clinical symptoms of active Crohn's disease.[26] In addition, synbiotics containing *Lactobacillus helveticus*, *Bifidobacterium infantis* and *Bifidobacterium bifidum*, and fructooligosaccharide have been found to limit common winter infections in schoolchildren.[27,28,29]

Hypercholesterolemia, or elevated levels of total cholesterol in the bloodstream, is the result of high levels of low-density lipoprotein (LDL) as compared to high-density lipoprotein (HDL) cholesterol.[33,39,40] Many Lactobacilli, being the natural inhabitants of the intestine, possess bile-salt hydrolase activity. This property has been used for developing probiotic formulations to combat hypercholesterolemia.

Of 15 available Cochrane reviews on probiotics, 10 of these review focus on luminal gastrointestinal conditions or infections, including infectious diarrhea, antibiotic-associated diarrhea, *C. difficile* colitis, inflammatory bowel diseases (including pouchitis), necrotizing enterocolitis in preterm infants, collagenous colitis, and irritable bowel syndrome.[24,25,26,27] Among these conditions, probiotics may reduce the risk of severe necrotizing enterocolitis in preterm infants weighing more than 1000 g; it also has utility in the maintenance of chronic pouchitis remission status post pouch-anal anastomosis.[25,28,29] Probiotics have also been found to be a useful adjunct to oral rehydration therapy for infectious diarrhea.[30] However, a more recent meta-analysis evaluating the use of probiotics in acute, likely infectious, diarrhea noted that the majority of the data was derived from hospital-associated studies, with a paucity of community-based trials of probiotic use in acute diarrhea and only one trial available from a developing world setting..[37,38]

Cochrane reviews of probiotic studies in antibiotic-associated diarrhea, *C. difficile* colitis, collagenous colitis, and irritable bowel

syndrome reported either no evidence of probiotic effectiveness in these conditions, or the available data were deemed insufficient to allow clear conclusions regarding efficacy.[31,32,33] Although various probiotic species have shown promise in the treatment of inflammatory bowel disease, given the small number of patients, differences in study durations and heterogeneity in these studies and the risks associated with probiotics, two systematic reviews have concluded that there is insufficient evidence to support the use of probiotics for the induction or maintenance of remission in inflammatory bowel disease. [32,33]

Prebiotic and probiotic therapy appear to lower blood ammonia concentrations, possibly by favoring colonization with acid-resistant, non-urease producing bacteria.[28,29,30] The most commonly used prebiotic for the treatment of hepatic encephalopathy is lactulose, though it also acts by altering the colonic pH, improving gastrointestinal transit, and increasing fecal nitrogen excretion.[29] Fermentable fiber is another prebiotic that may promote the growth of beneficial bacteria. Initial studies were associated with an improvement in hepatic encephalopathy. However, a large meta-analysis has shown no demonstrable benefit with regard to clinically relevant outcomes (e.g., mortality and quality of life). [31]

Two Cochrane reviews which addressed the role of probiotics in the prevention of allergic disease and food hypersensitivity in infants and the treatment of eczema, concluding that the probiotics studied were

either ineffective or there was insufficient evidence to recommend probiotic use at present in these conditions.[34,36,37] The remaining three Cochrane reviews evaluated probiotic use in the prevention of bacterial sepsis and wound complications in liver transplantation, treatment of nonalcoholic fatty liver disease, and prevention of preterm labor and concluded that the available data were similarly inconclusive.[41,42,43]

Pro-/pre-/synbiotics' potential anticancer activity has been mainly supported by a number of laboratory studies.[38,40] Alteration of the intestinal microflora composition/competition with the consumption of probiotics, reduction of intestinal inflammation (as well as of the mutagenic, carcinogenic and genotoxic compounds), elevation of immune response and increased short-chain fatty acid production have been proposed as potential chemopreventive mechanisms.[48,61]

A metagenomic analysis of 154 individuals, including monozygotic and dizygotic twins concordant for leanness or obesity, and their mothers also showed that obesity was associated with a relative depletion of Bacteroidetes and a higher proportion of Actinobacteria compared with leanness.[38,40,41,51] Consistently, one prospective study found that children with lower proportion of Bifidobacterium and higher levels of Staphylococcus aureus in their infancy gained significantly more weight at 7 years.[43,44]

Changes in energy harvesting from diet is also associated with the uptake of SCFAs, end products of bacterial fermentation: in obese humans, the amount of SCFAs in fecal samples was greater than in lean subjects, although the diets rich in nondigestible fibers decrease body weight and severity of diabetes; these contradictory findings could be explained by the anti-inflammatory effects of butyrate.[44,48,49] Furthermore, another pathway has been better studied in humans: the linkage between microbiota and systemic inflammation. LPS administration induces acute inflammation and systemic insulin resistance, stimulating the systemic and adipose tissue expression of proinflammatory and insulin resistance-inducing cytokines.[46]

Consistently in healthy human subjects, total energy intake and high-fat / high carbohydrate meals, but not fruit / fiber meals, can acutely increased plasma LPS levels, coupled with enhanced TLR4 expression.[22,46] The different pathophysiologic factors that explain the association of microbiota with metabolic disturbances have not been studied in depth in human in comparison with animal models, although growing evidences link gut microbiota with endotoxemia and energy harvest from diet

Several prebiotic and probiotic preparations have shown promise in preventing or treating various conditions. However, most studies have been small and many have important methodological limitations, making it difficult to make unequivocal conclusions regarding efficacy, especially

when compared with proven therapies. Furthermore, considerable differences exist in composition, doses, and biologic activity between various commercial preparations, so that results with one preparation cannot be applied to all probiotic preparations.

The appropriate therapeutic route, length of therapy, time of administration, and dosage of the probiotics and/ or synbiotics remain controversial issues

Probiotics, particularly lactobacilli, lactococci, and *Bifidobacterium*, are thought to be generally safe based on a long history of extensive use with likely daily ingestion by millions of individuals and limited reports of toxicity. Certain probiotic products have been studied in at-risk populations without reported toxicity or adverse outcomes. However, in general, there is insufficient information on most marketed probiotic preparations to provide assurances regarding safety.[37,39,40]

Although population-based studies appear reassuring about the toxicity of probiotic use, other data raise concerns about the use of at least certain probiotics in vulnerable patient populations, particularly immunocompromised hosts, the severely ill, those with serious comorbidities, patients with intravenous catheters, prosthetic material or hardware, short bowel syndrome, or abnormal cardiac valves, and the elderly.[21,22,38,42] In particular, a recent randomized, double-blind, placebo-controlled trial designed to evaluate the effectiveness of a probiotic

preparation (6 different *Lactobacillus* or *Bifidobacterium* strains; total daily dose 1010 bacteria) on infectious complications of acute pancreatitis reported increased mortality in the probiotic treatment group without any measurable impact on infectious complications.[42,43]

Further, bowel ischemia was significantly increased in the patients with acute pancreatitis treated with the probiotic. Bacteremia, endocarditis, and liver abscess have been reported as due to *Lactobacillus* spp. infection (including *L. rhamnosus* GG), with enhanced concern in individuals with short gut syndrome, central venous catheters, intestinal feeding tubes, or serious comorbidities.[38,39] Similarly, although *Saccharomyces boulardii* (brewer's yeast) is an infrequent fungal bloodstream isolate, in one series 86% of *S. boulardii* fungemia episodes were identified in children or adults who ingested *S. boulardii* as a probiotic.[31,33] Mortality or sepsis with shock has been reported as due to invasive infections associated with probiotic use. Other concerns about probiotic use, such as precipitating lactic acidosis, toxicity to the gastro-intestinal tract, and transfer of antibiotic resistance within the gastrointestinal tract, remain theoretical in the absence of substantiation in clinical studies or reports.[38,40,41,42,43]

Since probiotics contain live microorganisms, concurrent administration of antibiotics could kill a large number of the organisms, reducing the efficacy of the Lactobacillus and Bifidobacterium species. Patients should be instructed to separate the administration of antibiotics

from these bacteria- derived probiotics by at least two hours. [41,42] Similarly, S. boulardii might interact with antifungals, reducing the efficacy of this probiotic.[28] Probiotics should also be used cautiously in patients taking immunosuppressants, such as cyclosporine, tacrolimus, azathioprine, and chemotherapeutic agents, since probiotics could cause an infection or pathogenic colonization in immunocompromised patients [23,27,28,29]

Warfarin acts by blocking the intracellular activation of vitamin K. Intestinal bacteria produce a significant proportion of the vitamin K absorbed in the intestine locally, while antibiotics causing the disruption of the intestinal flora has been associated with symptomatic K vitamin deficiency and severe hemorrhage. [33,34,37,38] It is therefore conceivable that administration of bacteria that alter the local production of vitamin K could affect the sensitivity to warfarin and other vitamin K antagonists

While synbiotic combinations are considered to have beneficial effects on human health and medical conditions, their clinical value in surgical patients remains unclear given a paucity of applicable clinical studies. In a first ever surgical study on probiotics from South Asia, we attempt to assess the clinical usefulness of synbiotics in patients who undergo surgery for chronic pancreatitis.

AIM OF THE STUDY

AIM

The objective of the present investigation is to determine the impact of perioperative synbiotic therapy on

- postoperative infectious complications,
- first bowel movement,
- days in intensive care unit,
- length of hospital stay
- duration of antibiotic therapy
- mortality

in patients undergoing Frey procedure for Chronic Pancreatitis

REVIEW OF LITERATURE

REVIEW OF LITERATURE

There are 15 randomized, controlled clinical trials assessing the role of synbiotics in surgical patients which have been published so far.

Mixed abdominal surgery/colorectal surgery

Of the three studies which have been published, none have shown a significant positive effect of synbiotics in postoperative outcomes.[44,45,46] All three studies were performed by the same group. In the first study, 64 patients received pre- and postoperatively 107 Lactobacillus plantarum 299v plus oat fiber (Proviva, Skanemejerier, Malmö, Sweden). Compared to a placebo group (n= 65), there were no significant differences in the infection rates (13% versus 15%) and degree of bacterial translocation into mesenteric lymph nodes (12% versus 12%).

The second series included 72 patients who were perioperatively administered a synbiotic combination containing Lactobacillus acidophilus La5, Bifidobacterium lactis Bb-12, Streptococcus thermophilus, L. bulgaricus (Trevis, Christen Hansen, Denmark), and oligofructose, no significant differences were demonstrated with regards to infectious complications (32% versus 31%) and bacterial translocation (12%versus 11%). In the third study, 88 patients planned for colorectal surgery either received mechanical bowel preparation (MBP) alone,

neomycin plus MBP, neomycin plus MBP plus synbiotics, or neomycin plus synbiotics.[47]

The combination of MBP, neomycin, and synbiotics significantly reduced bacterial translocation (21%, 5%, 0%, and 18% respectively) and the amount of fecal Enterobacteriaceae, but this was not associated with a reduction in serum levels of CRP and IL-6 or septic morbidity (21%, 18%, 15%, and 14% respectively). The lack of effectiveness of synbiotics could be explained by the relatively short postoperative period of administration (median time 4 days), the route of administration with doubtful survival of the probiotics in the stomach, and the inhomogeneous distribution of operations with low-risk operations (simple colectomies) resulting in low overall rates of bacterial translocation and infections.

Rayes et al performed their study with synbiotics in mixed cohort of surgical patients (colectomies, resections of liver, stomach, and pancreas). Early enteral nutrition with nasojejunal administration of one probiotic (L. plantarum 299) and inulin as fiber was compared with enteral nutrition plus inulin alone or parenteral nutrition alone. Thirty percent in the parenteral group developed infections compared to 10% in the other two groups. Due to the inhomogeneous nature of the group, there was an unequal distribution of Operations with different risk rates.[48] The duration of administration was also very short (5days). Also, the results could have been influenced by the mode of nutrition, since bacterial infection rates in both groups with enteral nutrition were lower than in the

group with parenteral nutrition. However, a subgroup analysis of patients who underwent Whipple's procedure showed that these patients had the marked drop in infection rates from 50% to 14% in the group which was administered probiotics.

Pancreas resection

Studies show that infections rates among patients undergoing major pancreatic resections are 46-57%.[4,49,50,51] In a study from India, the infection rates were upto 60%.[5] These subset of patients have multiple risk factors for translocation and infection. Nomura et al. studied 64 patients scheduled for pancreaticoduodenectomy.[52] Of the 64 patients studied by Nomura et al, 30 received a probiotic mixture of Enterococcus faecalis T-110, Clostridium butyricum TO-A, and Bacillus mesentericus TO-A. There was a significant reduction of infectious complications (23% versus 53%), the median length of hospital stay was found to be significantly lower (19 days versus 24 days) and there was also a reduction in the percentage of patients who developed delayed gastric emptying (10% versus 20%). In another study from Berlin, 80 patients undergoing a pylorus preserving pancreatoduodenectomy (PPPD) were randomized to receive early enteral nutrition via nasojejunal route; 40 patients received a synbiotic cocktail of 1010 L. plantarum 2362, Lactobacillus paracasei subspecies paracasei F19, Leuconostoc mesenteroides 77:1, and Pediococcus pentosaceus 5-33:3 plus betaglucan, resistant starch, inulin, and pectin (Synbiotic 2000,

Medipharm, Kagerod, Sweden). In the group receiving synbiotics, the incidence of nosocomial bacterial infections was significantly lower (12.5% versus 40%), and only mild wound and urinary tract infections occurred.[49]

Acute pancreatitis

In a study from Hungary, forty-five patients with acute pancreatitis divided into two groups. One group received L. plantarum 299 plus oat fiber, while the other group received oat fiber plus heat-inactivated L. plantarum 299. There was a marked reduction in the number of patients who developed infected pancreatic necrosis, in the synbiotic group. [53,54.] In another study by the same group, Synbiotics with only fibers was administered to 62 patients with acute pancreatitis. The incidence of systemic inflammatory response syndrome and multiorgan failure (MOF) was significantly lower in the synbiotic group (8 versus 14 patients). [53,54] Even though not statistically significant, there was a lower incidence of MOF, septic complications, and mortality.

The first and, to date, the only surgical trial with serious adverse events of synbiotics was recently published by a Dutch group.[55] In a multicenter, double-blind, placebo-controlled trial, by the Dutch Pancreatitis group, 296 patients with predicted severe acute pancreatitis either received a synbiotic preparation consisting of 1010 L. acidophilus, L. casei, Lactobacillus salivarius, Lactococcus lactis, Bifidobacterium

bifidum, B. lactis plus cornstarch and maltodextrins (Ecologic 641, Winclove Bio Industries, Amsterdam, Netherlands) or placebo for 28 days together with fiber-enriched enteral nutrition. Even though the rates of infectious complications were comparable in both groups (30% versus 28%), the mortality rate was higher in the synbiotic group (16% versus 6%).

The main cause of death was bowel ischemia (eight patients). One likely explanation for these results is the fact that more patients in the synbiotic group had organ failures before or during the day of the first dose of treatment. (13.2% versus 4.9%). In addition, mortality rates in patients with severe acute pancreatitis are generally very high regardless of the type of treatment. An association between bowel ischemia and the synbiotic combination has been proposed as one of the causative factors.[51,55] Enteral feeding using high amounts of a fiber-enriched formula plus probiotics may lead to an increase in the intestinal oxygen consumption and ischemia in patients with organ failure, consecutive low blood pressure, and splanchnic hypoperfusion.

Liver resection

Upto 30% of patients undergoing liver resection, develop bacterial infections and 10% intraabdominal sepsis usually caused by enterogenic bacteria;[56] The incidence of infections rises markedly after extended resections(45%). [57] In cases where bacteremia is present, the risk of liver

failure rises to over 50% with a mortality of 40%. Limited hepatic clearance of lipopolysaccharides, excessive cytokine production of the liver, reduction of the function of the reticuloendothelial system, bile production, intestinal blood flow, and bowel motility are the reasons for bacterial translocation and infection.[57,58]

A study from Japan assessed the effect of synbiotics on the clinical course of extended liver resection for bile duct malignancy. The Intestinal microflora and liver function can interact in many different ways, a connection called gut–liver axis.[58,59] To study this axis, the impact of synbiotics on the clinical course of extended liver resection for bile duct carcinoma was evaluated. Twenty-one patients received enteral nutrition plus a synbiotic combination of 108 Bifidobacterium breve Yakult und L. casei Shirota (Yacult BL Seichoyaku, Japan) as well as galacto-oligosaccharides postoperatively for 14 days. In the synbiotics group, 19% had bacterial infections compared to 52% in the group without synbiotics.

A significant reduction of pathogenic bacteria and an increase of organic acids in the feces were observed. In another study by the same group, 81 patients operated for bile duct carcinoma were administered, high dose synbiotics either only postoperatively or 14 days preoperatively plus postoperatively. Perioperative treatment with synbiotics led to a significantly lower bacterial infection rate as compared to only postoperative treatment (12.1% versus 30%). An increased activity of

natural killer cells and a lower concentration of interleukin-6 levels in the blood as expression of a stimulation of the immune response and a reduction of the systemic inflammatory response were observed. [58,59]

Liver transplantation

Preoperative malnutrition, ascites, portal hypertension, transient loss of hepatic macrophage function which serves as a filter for Gram negative bacteria in the mesenteric circulation, the extended operation with potential extensive blood loss and manipulation and edema of the bowel, biliary complications, and the immunosuppression are few of the numerous risk factors for bacterial translocation, and infection. [51,60,61] Therefore, sepsis is the most important cause of death in liver transplant recipients. A 1-year organ survival was significantly decreased, and the hospital stay prolonged for 24 days costing an additional US $159.967 per patient.

Neuheus and colleagues published two studies, Ninety-five patients were enrolled in the first study. And received early enteral nutrition plus either selective bowel decontamination (SBD, group 1), a synbiotic combination with L. plantarum 299 (see before) and inulin as prebiotic (group 2), or inulin only (group 3). Bacterial infection rates were lower in the synbiotic group than in the other groups; the difference between groups 1 and 2 was statistically significant (48% versus 13%). Most of these infections were caused by enterogenic bacteria.

In a study of 66 liver transplant recipients who received a synbiotic combination with four probiotics and prebiotics (Synbiotic 2000) or only the prebiotics, only one patient (3%) had a bacterial infection compared to 48% in the other group. Additionally, even the duration of antibiotic therapy was significantly shorter (0.1 day versus 3.8 days). No severe side effects were observed in the studies; especially, no infections caused by the probiotics. [61].

MATERIALS AND METHODS

MATERIALS & METHODS

Study Design and Setting

At the Institute of Surgical Gastroenterology & Liver Transplantation, Govt. Stanley Medical College, Chennai, India a single blind prospective randomized placebo controlled clinical trial was conducted.

Randomization was computer generated using an on-site computer system with randomization software. The study was single blind, with the patients being blinded for the intervention. The study design was as presented in figure 1. The patients were assessed for eligibility using the inclusion and exclusion criteria (detailed below), and those who were planned for a Frey procedure were randomized. The patients in whom the surgery could not be completed were excluded from the study.

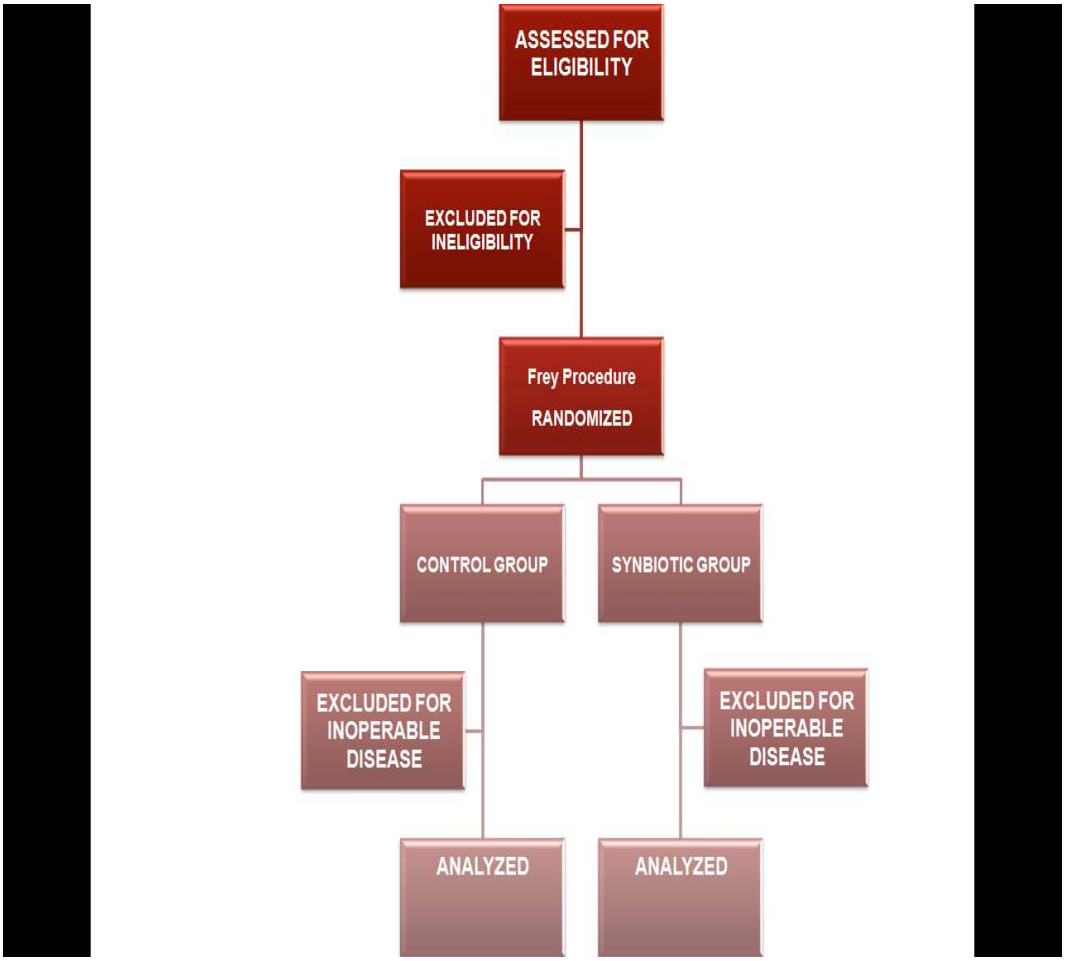

Figure 1: Study Design - Algorithm

Patients

All patients who were suffering from chronic pancreatitis and scheduled for Frey procedure were included in this prospective monocentric single-blind randomized control study.

Inclusion Criteria:

- All Adults between the ages of 18 and 75 years with good performance status (Karnofsky performance score >80).
- Patients with Chronic pancreatitis undergoing Frey Procedure

Exclusion criteria:

- Renal insufficiency defined as Creatinine > 1.1 mg/dl
- Presence of Intestinal obstruction
- Patients who underwent emergency surgery
- Patients with cerebral disorders with a danger of aspiration
- Any other contraindications for enteral nutrition.

Primary study endpoint:

Primary study endpoint fixed as the occurrence of postoperative infection during the first 30 days after surgery. The diagnosis of bacterial infection was based on systemic signs like fever (≥38°C), along with specific clinical symptoms of organ specific infection and a positive bacterial culture. Sources/sites of infection were specifically defined for the purpose of the study, based on international guidelines. Wound infections were defined as detection of pus in the wound along with a positive bacterial culture.

Respiratory infection was defined as fever, cough, dyspnea along with a reduced oxygen saturation, typical pulmonary infiltrate on chest x-ray, and a positive culture from sputum, or bronchoalveolar lavage. Peritonitis or intra-abdominal abscess was defined as fever with the presence of intra-abdominal pus and positive bacterial cultures from intra-abdominal smears. Sepsis was characterised as fever, low arterial blood pressure, systemic inflammatory response, and positive bacterial blood cultures. A diagnosis of Urinary tract infection made in the presence of dysuria, leukocyturia, and a positive urine culture with 10^5 colony forming units/mL.

Secondary study endpoints:

Secondary outcome measures were mortality, days to the first bowel movement after surgery, number of days in intensive care unit, total length of hospital stay and the total duration of antibiotic therapy.

Ethics, Informed Consent, Safety & Registration of Trial

The study was conducted in accordance with the principles of the Declaration of Helsinki and 'good clinical practice' guidelines. Approval from the Institutional ethics committee was obtained and all patients gave a written informed consent before inclusion in the trial. The study drug has been used in clinical practice for indications other than those indicated in the current study, its long history of usage in healthcare have shown a very good safety profile.

During administration of the drug both the patient and the nursing staff were required to register any potential side effects or adverse events. The criterion set to stop the study was withdrawal of patient consent and / or the occurrence of any serious adverse events owing to the administration of the drug.

As a testimonial to its bonafide nature, the study has been registered with *Clinical Trials Registry of India, National Institute of Medical Statistics, Indian Council of Medical Research, India. CTRI Number: CTRI/2013/06/003737*

Treatment program:

Patients' complete medical history and clinical examination, analysis of laboratory parameters, and disease-specific further examinations are evaluated. Serum albumin and body mass index are measured and calculated to evaluate the nutritional status. All patients are stratified using the classification of the American Society of Anesthesiologists. Patients are then individually randomized using randomization software to one of the two study groups.

Surgical Procedure

All patients undergoing chronic pancreatitis for Frey procedure were included. In brief, the procedure itself entails a formal laparotomy via a bilateral subcostal incision. The Duodenum is kocherised to completely mobilize the second part of the duodenum from the Inferior vena cava upto to the right border of the aorta. The gastrocolic omentum is divided to enter the lesser sac. The gastrocolic trunk is dissected, doubly ligated and divided.

The head, body and tail of pancreas are dissected and exposed. The pancreas is assessed for the presence of head mass and any other suspicious lesions. Based on the preoperative imaging or intraoperative Ultrasound, the pancreatic duct is localized in the region of the body to the left of the splenic vein-superior mesenteric vein confluence. The duct

is then laid open from tail upto the head. The pancreatic head and uncinate process are then cored out, to lay open the duct completely.

A roux –en- y limb of jejunum is fashioned and a side to side longitudinal pancreatico-jejunostomy is performed using a single layer braided/ monofilament suture in continuous or interrupted fashion. The abdomen is drained with bilateral flank drains and closed in layers. Intraoperative details like operative time, blood loss and any other significant intraoperative events are documented.

Study Groups

Group A

Specific composition of prebiotics and probiotics (synbiotics) { Streptococcus faecalis T-110 – 60 million, Clostridium butyricum TO-A – 4 million, Bacillus mesentericus TO-A – 2 million, Lactobacillus sporogenes – 100 million, Fructo-oligosaccharides was administered thrice daily via a feeding tube or orally. The treatment is started 5 days preoperatively and continued postoperatively for the first 10 days after surgery.

Group B

This group received identical treatment as group A, with the only difference being that the patients received only placebo. The contents of the placebo were specifically designed to be inert and to look identical to

the study drug. The smell and taste of the study substances were identical too. The persons who know the type of treatment were the nurse and the investigating clinician. The patients were completely blinded to the study randomization.

Regimen of Antibiotics and Catheters

All patients received a single dose of intravenous Cefuroxime (1.5 g) at induction as antibiotic prophylaxis. Following which the antibiotic was repeated if the procedure lasts more than 6 hours. Antibiotics were then started only in cases of bacterial infection. If there was a suspicion of infection, patients were initially treated empirically and then appropriate culture based antibiotics were started following resistance testing of the isolated bacteria. Proton pump inhibitors (Pantoprazole 40 mg) were routinely give twice daily as part of antiulcer prophylaxis.

During the operation, a central venous line was introduced, and a urinary catheterization was also done. These catheters were removed as soon as possible except in the rare case of serious complications.

Analyzed Parameters

Primary study endpoint was the occurrence of postoperative bacterial infection during the first 30 postoperative days after surgery. Therefore, the incidence, the type of infections, and type of isolated bacteria were specifically recorded. Secondary outcome measures

included mortality, first bowel movement, length of hospital stay, days in intensive care unit, and duration of antibiotic therapy. In addition, side effects which could be attributed to the synbiotics were evaluated.

The duration of antibiotic therapy was determined by counting the number of days for which the patients received antibiotic therapy. The single-shot of antibiotic prophylaxis which was administered peri-operatively was excluded. Total length of hospital stay was defined as the period from the day of the operation and to the day of discharge. To rule out any likely differences in the intraoperative and postoperative risk factors for the development of infections and to avoid a bias in the study, the relevant accompanying diseases, alcohol and nicotine use, antibiotic therapy 1 month prior to operation, operating time, and number of units of blood and blood products which were intraoperatively and postoperatively, were analyzed. Also evaluated were the lengths of stay in the intensive care unit, the first day of bowel movement after the surgery, and the type and duration of antibiotic therapy.

Diarrhea, constipation, vomiting, abdominal cramps, or distention and other side effects which could be attributed to the drug, were monitored daily until discharge. The presence of any other complications was also monitored daily. Blood samples were drawn preoperatively and on the postoperative days 1, 5, and 10. The following parameters were studied: complete blood count, renal function tests, serum electrolytes and

liver functions tests. Vital parameters in the form of temperature, pulse rate, blood pressure and respiratory rate were recorded serially.

In the presence of suspected infection, bacterial cultures from urine, blood, wound, and intra-abdominal drainages were done. The culture specimens were cultivated on agar plates for aerobic and anaerobic bacteria. Differentiation of bacteria, and antibiotic sensitivity testing was performed by using routine microbiological methods. Results of the cultures were reported, and only patients with clinical signs of infection along with positive cultures were treated with antibiotics.

Statistical Analysis

Statistical analysis was performed using the SPSS software (version 16.0. SPSS, Inc., Chicago, IL, USA). The extended chi-square test was used to compare specific variables. The Mann-Whitney *U* test and the Kruskal-Wallis test were used for non-parametric analysis of continuous distributed variables. *P* value *of* < 0.05 was considered statistically significant with a power of 80%.

The statistical analysis was performed at the Department of Biostatistics, Govt. Stanley Medical College, Chennai, India. A power analysis was performed to assess the required sample size and to avoid a type II error. From previous published literature and from our own data, it was assumed that perioperative synbiotics reduced the incidence of infectious complications from 50% to 12%. With alpha of 0.05 and power at 80%, along with a dropout rate of 10%, the calculated required sample size was 35 patients for each of the groups

RESULTS

RESULTS

Demographic and Operative Data

Four patients (all four in group B) were excluded from the study after randomization because Frey procedure was not possible due to the presence of active pancreatitis and extensive collaterals channels over the pancreas. All the other 75 randomized patients {Group A (n=39) and Group B (n=36)} completed the study. The two groups were homogenous with regards to demographic data; there were no differences in the age, gender, and American Society of Anaesthesiologists classification between the 2 groups (Table 1).

Postoperative Bacterial Infections

12.8% of the patients in Group A and 39% of patients in Group B had infective complications. Wound infections (n-3), respiratory infections (n-2) were observed in patients who were administered synbiotic. While in Group B apart from wound infection (n-8) and respiratory infection (n-3), urinary tract infection (n-2) and sepsis (n-1) were also observed. All infections were treated with antibiotics. This difference was statistically significant (*P*- 0.05). Most of the isolated bacteria were gut-derived with a predominance of *Klebsiella Pneumonia*, and *E. coli*.

Length of Hospital Stay and Antibiotic Therapy

There was no difference in mean operating times in group A(310 ± 46 min) and group B(321 ± 35 min**).** There was a blood loss in group A (271 ± 127 ml) and group B (258 ± 112 ml); no difference was noted in the two groups. There was no difference in the first bowel movement, and ICU stay in the two groups. The mean total length of hospital stay was shorter in group A (8.4 ± 2.9) as compared to group B (17.9 ± 5.2). The duration of antibiotic intake was also shorter in group A (2.4 ± 4.8) as compared to group B (10.8 ± 3.3), these differences were statistically significant ($p<0.05$).

Side Effects of Synbiotics

Synbiotic combinations were well tolerated in all patients.

Laboratory Parameters

The mean laboratory values including hemoglobin, total leukocyte count, blood urea nitrogen, serum bilirubin and serum albumin on postoperative period days one, five, ten, did not differ significantly throughout the two groups.

Table 1: Demographic Profile

	Group A n=25	Group B n=23	p-value
Gender (male/female)	15/10	14/9	NS
Age (years) {mean ± Standard error}	43.2±9.2	43.4±8.7	NS
BMI	22.3±3.2	21.9±3.4	NS
ASA			
1	10	9	NS
2	13	13	NS
3	2	1	NS

Table 2: Laboratory parameters –preoperative & postoperative.

		Preoperative	P value	POD 1	P value	POD 5	P value	POD 10	P value
Hemoglobin (gm/dl)	Group A	11.3 ± 1.2	NS	10.4 ± 1.3	NS	9.8 ± 1.1	NS	10.1 ± 1.1	NS
	Group B	11.4 ± 1.1		10.3 ± 1.2		9.6 ± 1.2		10.2 ± 1.3	
Leukocytes (cells/mm^3)	Group A	7800 ± 2100	NS	11400 ± 1300	NS	9.9 ± 2100	NS	9.8 ± 2500	NS
	Group B	7500 ± 2300		11700 ± 1500		10.2 ± 1900		10.1 ± 2600	
BUN (mg/dl)	Group A	30.3 ± 1.8	NS	24.3 ± 2.1	NS	24.1 ±2.2	NS	21.8 ± 1.2	NS
	Group B	32.1 ± 2.1		23.8 ±1.9		23.7 ± 1.8		22.1 ± 2.1	
Bilirubin (mg/dl)	Group A	1.2 ± 0.2	NS	2.8 ± 0.7	NS	2.1 ± 0.8	NS	1.7 ± 1.2	NS
	Group B	1.8 ± 0.5		2.6 ± 0.9		1.8 ± 1.1		1.8 ± 1.1	
Albumin (gm/dl)	Group A	3.8 ± 1.1	NS	3.3 ± 1.1	NS	3.6 ± 1.2	NS	3.6 ± 0.9	NS
	Group B	3.6 ± 1.2		3.5 ± 0.9		3.6 ± 1.1		3.5 ± 1.2	

Expressed as Mean ± Standard error of mean

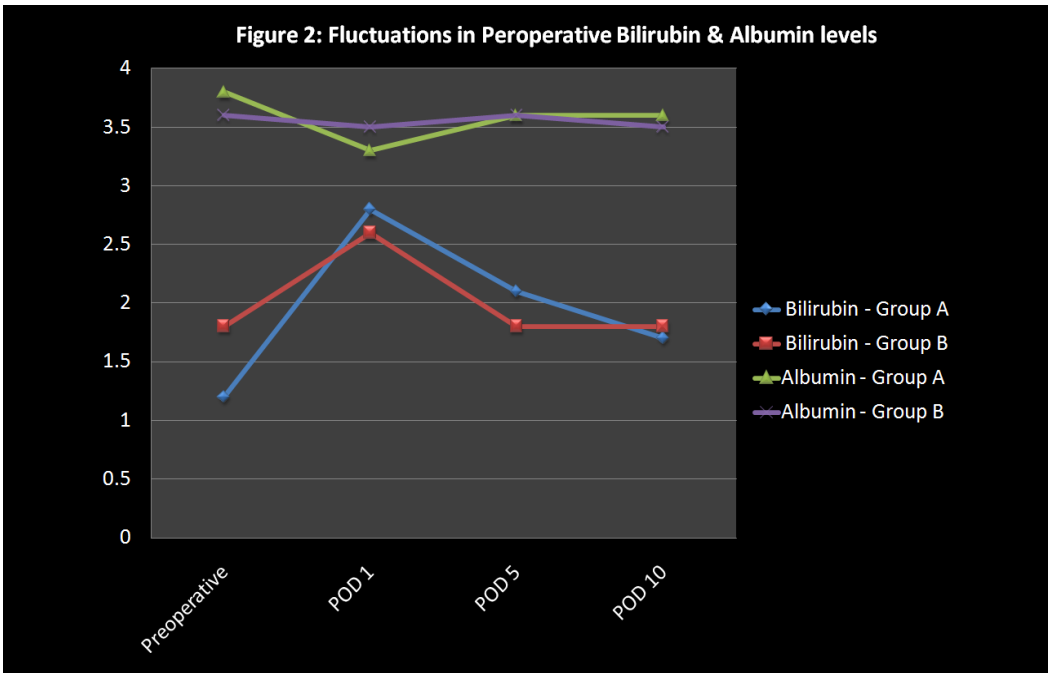

Table 3: Infective Complications

	Group A n=39	Group B n=36	P Value
Infections	5 (12.8%)	14(39%)	P < 0.05
Wound	3	8	
Respiratory	2	3	
Urinary Tract	0	2	
Sepsis	0	1	
Organisms			
Klebsiella Pneumonia	3	7	
Escherichia Coli	2	4	
Methicillin Resistance Staphyloccocus aureus	-	1	
Acinetobacter calcoaceticus	-	1	
Coagulase Negative Staphyloccocus aureus	-	1	

Figure 3: Infective Complications

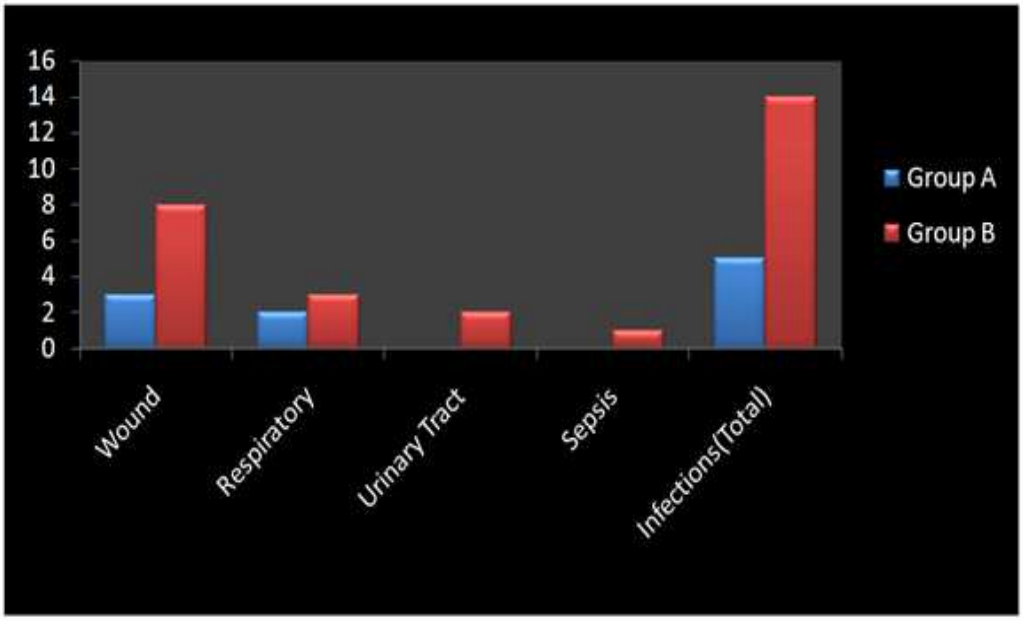

Table 3: Operative Data & Postoperative variables

	Group A	Group B	P value
Operating Time	310 ± 46	321 ± 35	NS
Blood Loss (ml)	271 ± 127	258 ± 112	NS
First Bowel Movement (days)	3.2 ± 2.1	3.4 ± 2.9	NS
ICU stay (days)	4.3 ±3.1	4.2 ± 2.2	NS
Hospital (days)	8.4 ± 2.9	17.9 ± 5.2	P < 0.05
Antibiotics (days)	2.4 ± 4.8	10.8 ± 3.3	P < 0.05

Expressed as Mean ± Standard error of mean

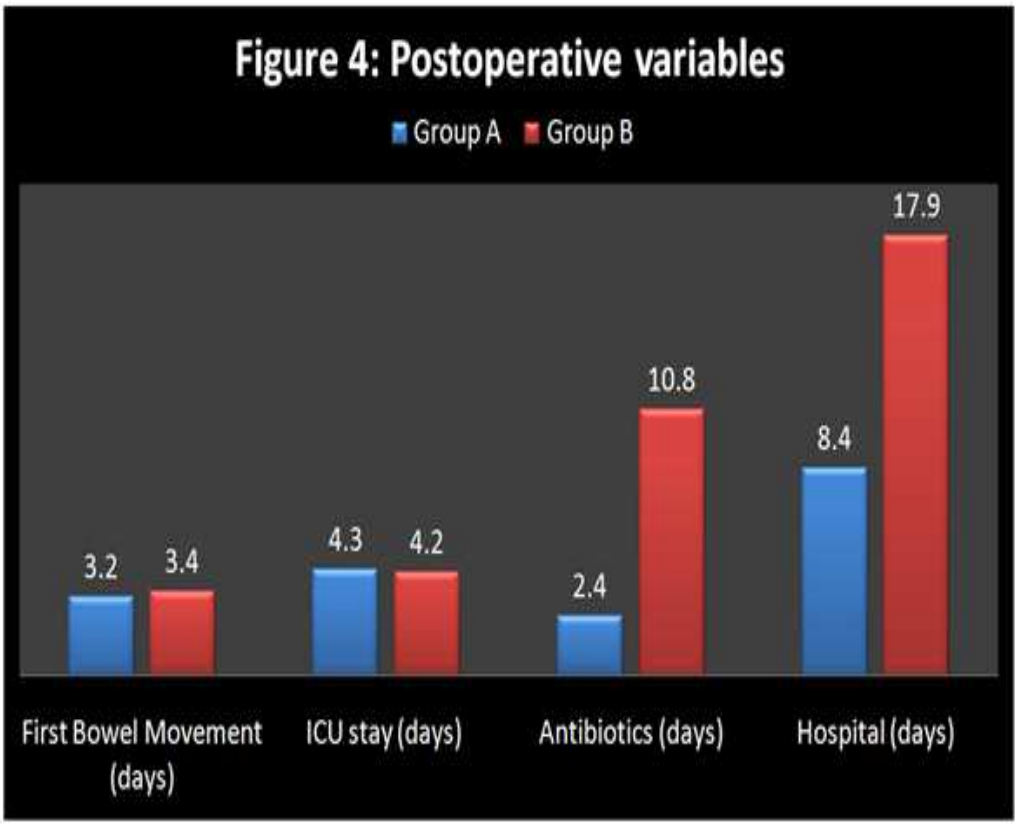
Figure 4: Postoperative variables
Group A
Group B
3.2
3.4
4.3
4.2
2.4
10.8
8.4
17.9
First Bowel Movement (days)
ICU stay (days)
Antibiotics (days)
Hospital (days)

DISCUSSION

DISCUSSION

Ours is the first randomized control trial in South Asia to evaluate the efficacy of synbiotics in the reduction of infectious complications in patients undergoing pancreatic surgery.

Frey procedure was chosen as the target surgery for four important reasons. This procedure involves a defunctioned limb of jejunum, hence any anastomotic leak will not interfere in patients alimentation. It will also avoid skewing of data due to any infective complications due to the leaking anastomosis. Frey procedure involves coring out of the head of pancreas; hence it involves undergoing major stress on the part of the patient, thereby replicating the milieu which would occur during head resection procedures like the Whipple procedure. This would allow extrapolation of data and results accrued in this study to other pancreatic surgery. The final reason why Frey procedure was chosen for this study was that, it is a very commonly performed procedure in this part of the country where chronic calcific pancreatitis is endemic. Any reduction in infectious complications and morbidity in this subset of patients will be beneficial to the patient, healthcare sector and to the society in general.

This study shows that perioperative synbiotic treatment decreased the rate of postoperative infectious complications after pancreatic surgery without any adverse effect.

Patients undergoing pancreatic resection have multiple risk factors for bacterial translocation and infection leading to bacterial infection rates of upto 61% [3,4] Recent data on overall bacterial infection rates in pancreatic surgery range between 30% and 50% despite advanced surgical techniques, broad-spectrum antibiotic prophylaxis, and treatment. [5,6] Our own data accrued over the past five years, have shown the infectious complications rates to be in the range of 50%. In the present prospective, randomized, double-blind trial, synbiotic combination significantly reduced this incidence of bacterial nosocomial infections to 12.8%.

There were no significant differences between the groups with regards to important risk factors for the development of infections like advanced age, comorbidities, operative time or a large number of intraoperatively and postoperatively transfused blood products. In addition, the number of patients with surgical complications was same in both groups. Besides reduction of infection rates, these patients had a strong tendency towards a shorter hospital stay, and a significantly shorter duration of antibiotic therapy, which led to a reduction of the costs.

Nomura et al showed that probiotics led to significant reductions in infectious complications (23% versus 53%) and median length of hospital stay (19 days versus 24 days) following pancreatic surgery. [52] A double blind randomized study in patients undergoing pylorus preserving pancreaticoduodenectomy from Berlin, concluded that the incidence of nosocomial bacterial infections was significantly lower (12.5% versus 40%), and only mild wound and urinary tract infections occurred in those who were administered perioperative probiotics. [49]

The PROPARTRIA trial conducted in patients with severe pancreatitis showed serious adverse events of synbiotics. [55] The rate of infectious complications was comparable in both groups (30% versus 28%), but the mortality rate was higher in the synbiotic group (16% versus %). This was the first study which showed, synbiotics are not always beneficial. There have been a few criticisms about the PROPARTRIA trial. The patients in the Dutch study were on the average 15 years older than those patients in the previous pancreatitis studies, and there was a higher frequency of biliary pancreatitis which tends to be more severe than ethanol-induced pancreatitis. Greater severity of illness and Systemic Inflammatory Response Syndrome was suggested by higher Imrie scores and C-Reactive Protein levels in the Besselink study, but this was offset by lower APACHE II scores and a lower percentage of pancreatic necrosis on CT scan compared to the other studies.49,55

The Dutch patients received a greater number of probiotic organisms (six types of both Lactobacillus and Bifidobacteria at 1010 CFU/mL (versus one to four types of Lactobacillus alone in the Olah studies). Patients were treated with probiotics for a longer period in the Besselink study (4 weeks compared to 1 week in the Olah studies), and the Dutch researchers were very aggressive with the probiotic/enteral nutrition therapy (as evidenced by the fact that feedings were continued on pressor agents in some patients). Factors such as older age, under-resuscitation, hypoperfusion on pressor therapy, and greater disease severity may make the risk prohibitive in certain patients.[49,54,55]

Reasons for the adverse outcome of the Dutch study include an 85% reduction in the blood supply to the mucosa in patient with acute pancreatitis, leading to intestinal hypoperfusion.[49] It is known that intestinal epithelia under metabolic stress perceive commensal bacteria as a threat, leading to increased local inflammation. Therefore, the combination of severe pancreatitis, organ failure, intestinal hypoperfusion, and an increased (probiotic) bacterial load could have lead to increased local inflammation, further compromising mucosal blood supply. Another cause could be the increased oxygen demand and/or accumulation of fermentation products associated with the presence of probiotics, which could have lead to a barrier dysfunction within the gut.

Studies from Japan investigating the impact of synbiotics on the clinical course of extended liver resection have shown a significant

reduction in bacterial infections (19% vs. 52%). [50,56,57,58] Studies from Europe conducted on patients undergoing colorectal and abdominal surgery have shown equivocal results.

Current evidence suggests that synbiotic treatment is promising in maintaining and repairing the gut microbiota and gut environment, it also significantly reduces septic complications in patients with severe systemic inflammatory response syndrome (SIRS).[39,40] Finally, despite the promising clinical results with the use of these therapies, the mechanisms of action in the gastrointestinal tract remain undefined. Further clinical research is necessary to clarify the effectiveness of such therapies and define the appropriate conditions for use, before indiscrete widespread application of synbiotics in the perioperative setting. [40,48,49]

With its environmental, social, cultural and dietary distinctiveness, it might not be entirely appropriate to extrapolate western data onto the south-Asian subset of the population. Furthermore, there are no clinical trials from south east Asia, and the effectiveness of synbiotics in this population remains to be assessed.[63, 64]

Limitations of the study:

Even though a prospective randomized trial, this study does suffer from a few drawbacks. The synbiotic used was a multibacterial combination synbiotics; this study did not perform an analysis between the varied types of synbiotics and their effect. This would have given a true idea as to how efficacious each synbiotic actually is. Although a power analysis was done, the sample size is small; this might have led inadvertent concealment of differences between the two groups.

The lack of infection in the synbiotic group might by the result of type I error. The duration of administration of the synbiotics were empirical, there is no evidence to suggest if a shorter or a longer duration might be beneficial, this needs to be looked at before, guidelines can be formulated on the regular usage of synbiotics perioperatively. Frey procedure might be a true representation of pancreatic surgery, but there is no data on how synbiotics might affect outcomes after other pancreatic operations.

Further studies are required to investigate the mechanism of synbiotic treatment in combination with changes in intestinal flora and organic acid concentration and the associated decrease in postoperative infectious complications. A multicenter, prospective randomized trial using different synbiotics formulations would be required to answer the questions raised in this study.

CONCLUSION

CONCLUSIONS

- In patients undergoing pancreatic surgery for Chronic Pancreatitis

Synbiotics significantly reduce

- infective complications
- hospital stay
- antibiotic requirement

Synbiotics did not influence

- Day to first bowel movement
- length of ICU stay
- Peroperative haematological and biochemical parameters

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ANNEXURES

TO PARTICIPANTS AND CONSENT FORM

Name of Participant: _____

Title: IMPACT OF PERIOPERATIVE ENTERAL SYNBIOTICS IN SURGERY FOR CHRONIC PANCREATITIS: *A SINGLE BLIND PROSPECTIVE RANDOMIZED CONTROL TRIAL*

You are invited to take part in this research study. The information in this document is meant to help you decide whether or not to take part. Please feel free to ask if you have any queries or concerns. You are being asked to participate in this study being conducted in Govt. Stanley Medical College Hospital because you satisfy our eligibility criteria

What is the purpose of research?

Postoperative infections occur despite the improvements in surgical techniques and refinements in perioperative care. The majority of the observed infections are caused by bacteria from the gut, which translocate (move) from the intestinal lumen into the blood stream. Probiotics (harmless living bacteria- normally found in the intestines) are able to influence all pathogenic mechanisms of bacterial translocation. Prebiotics are nondigestable food constituents that selectively alter growth or activity of one or a limited number of bacterial species. Therefore, prebiotics and probiotics are potentially useful in prevention of bacterial infections. Used in combination, probiotics and prebiotics are called synbiotics. While symbiotic combinations are considered to have beneficial effects on human health, their clinical value in surgical patients remains unclear given a paucity of applicable clinical studies.

In this study we assess the clinical usefulness of synbiotics in patients who undergo hepatic and pancreatic resections with an aim to

assess a reduction in infective complications. Information obtained from this study would be beneficial to other patients with hepatic or pancreatic surgeries in the future. We have obtained permission from the Institutional Ethics Committee for conducting this study.

The study design

You will be one of the 120 patients we plan to recruit in this study. You will be assigned to either of the two study groups. You will be "randomized" into one of the study groups described below. Randomization means that you are put into a group by chance. A computer program will place you in one of the study groups. Neither you nor your doctor can choose the group you will be in. Which treatment group you will be assigned to will be determined purely by chance, which, in scientific language, is called “randomization”. Randomization improves the scientific quality of research. You will have an equal chance of being placed in any group.

One group of patients will receive the synbiotic medication, while the other group of patients will receive placebo. A placebo is an inactive or a dummy medication, which is given to increase the scientific validity of our study. Moreover, a placebo is needed so that it does not become to which group you are being assigned. This method, in scientific terms is known as blinding. This is important for unbiased evaluation of the study medication.

Study Procedures

Complete medical history and clinical examination, analysis of laboratory parameters, and disease-specific further examinations are

done. Patients are then individually randomized using randomization software to one of the 2 study groups.

Surgical Procedure

All major pancreatic resection surgeries included in the study (Whipple procedure, Distal pancreatectomy, Frey procedure). All Hepatic resections surgeries are included in the study.

Study Groups

Group A

Specific synbiotic composition of prebiotics and probiotics is administered thrice daily via the feeding tube or orally. The treatment started 5 days preoperatively and continued during the first 10 days after surgery.

Group B

Identical treatment as group A, with the only difference being that the patients receive only placebo, the contents look identical in both groups. The smell and taste of the study substances are identical, too.

Blood tests will be taken before the surgery and on the first, fifth and tenth day postoperatively, apart from routine/indicated disease specific blood tests. These tests are essential to monitor your condition, and to assess the safety and efficacy of the treatment given to you.

Possible risks to you

Since these are harmless bacteria normally found in the intestines, there are very few adverse effects. Some of the common adverse effects of the drug which will be given to you, include abdominal pain, vomiting and bloating.

In case of injury or a medical problem during this research study

Your safety is the prime concern of the research. If you are injured or have a medical problem as a result of being in this study, you should contact one of the people listed at the end of the consent form. You will be provided the required care/treatment.

Confidentiality of the information obtained from you

You have the right to confidentiality regarding the privacy of your medical information (personal details, results of physical examinations, investigations, and your medical history). By signing this document, you will be allowing the research team investigators, other study personnel, sponsors, institutional ethics committee and any person or agency required by law to view your data, if required. The results of clinical tests and therapy performed as part of this research may be included in your medical record. The information from this study, if published in scientific journals or presented at scientific meetings, will not reveal your identity.

How will your decision to not participate in the study affect you?

Your decision not to participate in this research study will not affect your medical care or your relationship with the investigator or the institution. Your doctor will still take care of you and you will not lose any benefits to which you are entitled.

Can you decide to stop participating in the study once you start?

The participation in this research is purely voluntary and you have the right to withdraw from this study at any time during the course of the study without giving any reasons. Though advisable that you give the investigators the reason for withdrawing, it is not mandatory.

Right to new information

If the research team gets any new information during this research study that may affect your decision to continue participating in the study, or may raise some doubts, you will be told about that information.

PATIENT CONSENT FORM

IMPACT OF PERIOPERATIVE ENTERAL SYNBIOTICS IN SURGERY FOR CHRONIC PANCREATITIS: *A SINGLE BLIND PROSPECTIVE RANDOMIZED CONTROL TRIAL*

Name of the participant: _____

Name of the Principal (Co-) Investigator: _____

Name of the Institution: Govt.Stanley Medical College Hospital

Documentation of the informed consent

I, ... have read the information in this form (or it has been read to me). I was free to ask any questions and they have been answered. I am over 18 years of age and, exercising my free power of choice, hereby give my consent to be included as a participant in "**Impact Of Perioperative Enteral Synbiotics In Surgery For Chronic Pancreatitis: *A Single Blind Prospective Randomized Control Trial*".**

(1) I have read and understood this consent form and the information provided to me.

(2) I have had the consent document explained to me.

(3) I have been explained about the nature of the study.

(4) My rights and responsibilities have been explained to me by the investigator.

(5) I have been advised about the risks associated with my participation in the study.

(7) I agree to cooperate with the investigator and I will inform

him/her immediately if I suffer unusual symptoms.

(8) I am aware of the fact that I can opt out of the study at any time without having to give any reason and this will not affect my future treatment in the hospital.

(9) I am also aware that the investigators may terminate my participation in the study at any time, for any reason, without my consent.

(10) I hereby give permission to the investigators to release the information obtained from me as result of participation in this study to the sponsors, regulatory authorities, Government agencies, and ethics committee. I understand that they may inspect my original records.

(11) My identity will be kept confidential if my data are publicly presented.

(12) I have had my questions answered to my satisfaction and I have decided to be in the research study.

I am aware, that if I have any questions during this study, I should contact at one of the addresses listed above. By signing this consent from, I attest that the information given in this document has been clearly explained to me and apparently understood by me. I will be given a copy of this consent document.

Name and signature / thumb impression of the participant

_____(Name) _____(Signature) Date: _

Name and signature of impartial witness (required for illiterate patients):

_____(Name) ____(Signature) Date:__

Name and signature of the Investigator or his representative obtaining consent:

_____(Name) _____(Signature) Date:_____

நோயாளி தகவல் தாள்

கல்லீரல் மற்றும் கணைய அறுவை சிகிச்சையில் சின்பயோடிக் எனும் குடல்வழி மருந்தின் பயன்கள் மற்றும் விளைவுகள். இது ஒரு ஒரே முறையில் பயன்களையும், விளைவுகளையும் அறிந்து கொள்ள உதவும் ஆராய்ச்சி.

IMPACT OF PERIOPERATIVE SYNBIOTICS IN SURGERY
FOR CHRONIC PANCREATITIS:
A SINGLE BLIND PROSPECTIVE RANDOMIZED CONTROL TRIAL

உங்களை இந்த ஆராய்ச்சியில் பங்கு கொள்ள அழைக்கிறோம். நாங்கள் உங்களுக்கு கொடுக்கும் இந்த படிவத்தில் உள்ள விவரங்களை கொண்டு, நீங்கள் இந்த ஆராய்ச்சிக்கு உட்படலாமா (அ) நிராகரிக்கலாமா என்பதை நீங்களே முடிவு செய்யலாம். மேலும் உங்களின் சந்தேகங்களையும், விளக்கங்களையும் எங்களிடம் கேட்கலாம்.

நீங்கள் எங்கள் ஆராய்ச்சிக்கு தகுதி உள்ளவராகும் பட்சத்தில், அரசு ஸ்டான்லி மருத்துவமனையில் நடைபெறும் இந்த ஆராய்ச்சியில் உங்களை பங்கெடுத்துக் கொள்ள செய்வோம்.

ஆராய்ச்சியின் நோக்கம் :

அறுவை சிகிச்சை முறையிலும் அதற்கு முன், பின் சிகிச்சை முறையிலும், சிறப்புடைய மேம்படுத்த நடைமுறைகளை கையாண்டும், அறுவை சிகிச்சைக்குப் பின் ஏற்படும் தொற்றினை முழுமையாக நீக்க இயலவில்லை. இந்த தொற்றுக்கு மிக முக்கிய காரணம் என்னவென்றால்,

அறுவை சிகிச்சையின் போது குடலில் உள்ள நுண்கிருமிகள் இரத்தத்தில் இடம் பெயறுவதால் தான் **புரோபயோடிக்** என்பது குடலில் உள்ள நன்மை பயக்கும் நுண்கிருமிகள். இவைகள் இரத்தத்தில் கலக்கும் நுண்கிருமிகளை ஊக்குவிக்கின்றன.

பிரிபயோடிக் என்பது ஜீரணிக்கப்பட முடியாத உணவு வகையை சேர்ந்த ஒரு பொருள். இது சில குறிப்பிட்ட நுண்கிருமிகளை வளரச் செய்யக் கூடிய அல்லது அதன் செயல்களை கட்டுப்படுத்தக் கூடிய அல்லது அதன்

எண்ணிக்கையை குறைக்கக் கூடிய ஆற்றல் உள்ளது. **புரோபயோட்டி** க்கும் **ப்ரிபயோடிக்கும்** இணைந்தம் **சின்பயோடிக்** என்று அழைக்கப்படுகிறது.

இந்த **சின்பயோடிக்** மனித ஆரோக்கியத்திற்கு பல நன்மைகளை அளிக்கிறது. ஆனால் அறுவை சிகிச்சையில் இதன் பயன்களைப் பற்றி ஆராய்ச்சி மூலம் நாம் சொற்பமான அளவே அறிந்துள்ளோம்.

இந்த ஆராய்ச்சியின் மூலம் நாங்கள் கல்லீரல் மற்றும் கணைய அறுவை சிகிச்சையின் போது **சின்பயோடிக்** உபயோகிப்பதால் அறுவை சிகிச்சைக்குப் பின் ஏற்படும் தொற்று குறைகிறதா என்பதை கண்டு அறிவது ஆகும். இதன்மூலம் எங்களுக்கு கிடைக்கும் விவரங்கள், பின்வரும் காலங்களில் கல்லீரல் மற்றும் கணைய அறுவை சிகிச்சைக்கு வரும் நோயாளிகளுக்கு பயனுள்ளதாக இருக்கும்.

இந்த ஆராய்ச்சியை மேற்கொள்ள இம்மருத்துவமனையில் உள்ள நெறிமுறைகுழு அனுமதி வழங்கியுள்ளது.

ஆராயச்சி வடிவமைப்பு :

நாங்கள் இந்த ஆராய்ச்சிக்காக உட்படுத்தப்படும் 120 நோயாளிகளில் நீங்களும் ஒருவர். நாங்கள் இரண்டாக பிரிக்கும் ஏதாவது ஒரு பிரிவில் நீங்கள் இருப்பீர்கள். நீங்கள் எந்த பிரிவில் இருப்பீர்கள் என்பது கணினி மூலம் ஏற்படுத்தப்பட்ட நிகழ்வாகும். நீங்களோ அல்லது மருத்துவரோ இதை முடிவுசெய்ய இயலாது. நீங்கள் எந்த பிரிவில் இருப்பீர்கள் என்பது உங்களுக்கு கணினி மூலம் கிடைக்கும் வாய்ப்பு. இவ்வாறு செய்வதால் ஆராய்ச்சியில் அறிவியல் தரம் மேன்மை அடைகிறது. நீங்கள் இந்த இரண்டு பிரிவுகளில் எந்த பிரிவில் இடம் பெறுவதற்கும் சமமான வாய்ப்பு உண்டு.

முதல் பிரிவில் உள்ள நோயாளிகள் **சின்பயோடிக்** மருந்து குளிக்கு பெறுவர். மற்றொரு பிரிவில் உள்ளவர்கள் மருந்தற்றகுளிகையை பெறுவர். இவ்வாறு ஆராய்ச்சி செய்வதால்தான் இந்த ஆராய்ச்சியின் மதிப்பு உயரும். இரண்டு பிரிவுகளுக்கும் மருந்து குளிகை கொடுத்தால்தான், தான் எந்த பிரிவில் உள்ளோம் என்பது நோயாளிக்குத் தெரியாது. இந்த செய்கை **சின்பயோடிக்** குளிகையை நடுநிலையாக மதிப்பாய்வு செய்ய மிகவும் முக்கியயமானது.

ஆராயச்சி முறை:

❖ முழுமையான மருத்துவ வரலாறு, மருத்துவ பரிசோதனை, ஆய்வக பரிசோதனை மற்றும் நோய்க்கு ஏற்புடைய சில பரிசோதனைகள் செய்யப்படும்.

❖ நீங்கள் கணினி மென்பொருள் மூலம் தேர்தெடுக்கப்பட்ட ஒரு குழுவில் இடம் பெறுவீர்கள்.

❖ எல்லா வகையான கணைய அறுவை சிகிச்சை, கல்லீரல் அறுவை சிகிச்சை மேற்க்கொள்ளப்படும் நோயாளிகள் இதில் இடம் பெறுவீர்கள்.

பிரிவு-1 :

இந்த பிரிவில் உள்ளவர்களுக்கு குறிப்பிட்ட அளவு உள்ள **சின்பயோடிக்** மருந்து ஒரு நாளைக்கு மூன்று முறைவாய்வழியாக அல்லது உணவு திரங்கள் செலுத்தும் குழாய் மூலமாக கொடுக்கப்படும். இது அறுவை சிகிச்சைக்குப் முன் 5 நாட்களும் அறுவை சிகிச்சைக்கு பின் 10 நாட்களுக்கு அளிக்கப்படும்.

பிரிவு-2 :

இந்த பிரிவில் உள்ளவர்களுக்கும் மேற்கண்டவாறேசெய்யப்படும். ஆனால் குளிகையில் மருந்து இருக்காது இரண்டு பிரிவுகளுக்கும் கொடுக்கும் குளிகையானது தோற்றத்தில் வாசனையில், ருசியில் ஒரே மாதிரியாக இருக்கும்.

அறுவை சிகிச்சை முடிந்த, 1, 5 மற்றும் 10 ஆம் நாட்கள் சில இரத்த பரிசோதனைகள் செய்யப்படும். இது உங்களுக்கு செய்யப்படும் சில வேண்டிய பரிசோதனைகளில் இருந்து வேறுபட்டதாகும். இந்த பரிசோதனைகள் உங்கள் உடல்நிலை கண்காணிப்பதற்கும் மேலும் உங்களுக்கு அளித்த சிகிச்சையின் பாதுகாப்பு தன்மைக்கும், ஆற்றலுக்கும் மிகவும் தேவை.

உங்களுக்கு ஏற்படக்கூடிய சில பொதுவான சந்தேகங்களும் அதற்கான பதில்களும் :

கேள்வி எண்-1 :

இந்த மருந்தை உட்கொள்வதால் எனக்கு ஏதேனும் பக்க விளைவுகள் ஏற்படுமா?

பதில் :

நமது குடலில் உள்ள தீமையற்றநுண்கிருமியை போலவே, இக்குளிகையிலும் உள்ளதால் மிக சொற்பமான அளவே சில பக்க விளைவுகள் ஏற்படும். அவையாவன **வயிற்றுவலி, வாந்தி மற்றும் வயிறு உப்புசம்.**

கேள்வி எண்-2 :

எனக்கு ஏதாவது மருத்துவ ரீதியான பிரச்சனைகளோ (அ) பின் விளைவுகளோ இந்த ஆராய்ச்சிக்கு உட்படுவதால் ஏற்படுமா?

பதில் :

உங்களுடைய பாதுகாப்பு எங்களுடைய முதல் மற்றும் தலையாய கடமை. உங்களுக்கு ஏதாவது மருத்துவரீதியான பிரச்சனைகள் ஏற்ப்பட்டால் நீங்கள் இந்த ஒப்புதல் படிவத்தில் கொடுத்துள்ள நபர்களை எந்த நேரத்தில் வேண்டுமானாலும் அணுகலாம்.

உங்களுக்குத் தேவையான கவனிப்பும், சிகிச்சையும் அளிக்கப்படும்.

கேள்வி எண்-3 :

என்னிடம் இருந்து பெறப்பட்ட தகவல் பாதுகாக்கப்படுமா?

பதில் :

உங்கள் மருத்துவ பதிவேடுகள் மிகவும் அந்தரதங்கமாக வைத்துக் கொள்ளப்படும் மற்றும் பிறமருத்துவர்கள் / விஞ்ஞானிகள் / இந்த ஆய்வின் தணிக்கையாளர்கள் (அ) ஆராய்ச்சி ஆதரவாளர்களின் பிரதிநீதிகள் ஆகியோரிடமும் அவை வெளிப்படுத்தப்படும். இந்த ஆய்வின் முடிவுகள் அறிவியல் பத்திரிக்கைகளில் பிரகரிக்கப்படலாம். இந்த ஆய்வின் முடிவுகளை மூலம் நீங்கள் அடையாளம் காட்டபட மாட்டீர்கள்.

கேள்வி எண்-4 :

நான் இந்த ஆராய்ச்சியில் பங்கேற்கவில்லை என்றால் எனக்கு ஏதேனும் பாதிப்பு வருமா?

இந்த ஆய்வில் உங்கள் பங்கேற்பு தன்னிச்சையானது மற்றும் காரணங்கள் கூறாமலே நீங்கள் இந்த ஆய்வில் இருந்து விலகிக் கொள்ளலாம். உங்கள் உடல்நிலைக்கேற்ப பொருத்தமான சிகிச்சை அளிக்கப்படும்.

கேள்வி எண்-5 :

நான் ஆராய்ச்சிக்கு சம்மதித்த பிறகு விலகிக் கொள்ளலாமா?

பதில் :

எந்த ஒரு நேரத்திலும் நீங்கள் மோசமாக உணர்ந்தாலோ (அ) உடல்நலக்குறைவு உண்டானாலோ நீங்கள் இந்த ஆராய்ச்சியில் இருந்து விலகிக் கொள்ளலாம்.

கேள்வி எண்-6 :

இந்த ஆராய்ச்சியின் போது ஏதேனும் புதிய தகவல்கள் கிடைத்தால் அதை எனக்கு அறிவிப்பீர்களா?

ஆய்வின் போது ஏதேனும் புதிய தகவல்கள் தெரிய வந்தால் அதைப்பற்றி உங்கள் மருத்துவர் உங்களுக்கு தெரிவிப்பார்.

நோயாளி சம்மத படிவம்

கல்லீரல் மற்றும் கணைய அறுவை சிகிச்சையில் சின்பயோடிக் எனும் குடல்வழி மருந்தின் பயன்கள் மற்றும் விளைவுகள். இது ஒரு ஒரே முறையில் பயன்களையும், விளைவுகளையும் அறிந்து கொள்ள உதவும் ஆராய்ச்சி.

IMPACT OF PERIOPERATIVE SYNBIOTICS IN SURGERY
FOR CHRONIC PANCREATITIS:
A SINGLE BLIND PROSPECTIVE RANDOMIZED CONTROL TRIAL

நோயாளியின் பெயர் .....

வயது ..... வருடங்கள் அல்லது பிறந்த தேதி .....

நோயாளியை தொடர்பு கொள்ளும் முகவரி .....

.....

.....

நோயாளியின் தொலைபேசி எண்.

நோயாளியின் இன்சியல்ஸ் ..... பாலினம் ஆண் ..... பெண் .....

		பங்கேற்பவரின் இன்சியல்/பெரு விரல் பதிப்பு
1)	மேல் குறிப்பிடப்பட்டுள்ள ஆய்வின் ..... தேதியிட்ட நோயாளிகளுக்கான செய்தி நான் படித்திருக்கிறேன் மற்றும் புரிந்திருக்கிறேன்/ விவரிக்கப்பட்டுள்ளேன். கேள்விகள் கேட்கவும் அனுமதி வழங்கப்பட்டுள்ளேன் என நான் உறுதி செய்கிறேன்.	
2)	இந்த ஆய்வில் பங்கேற்பது என் சொந்த விருப்பப்படியே என நான் புரிகிறேன். மேலும் என் மருத்துவ சிகிச்சை கவனிப்பு அல்லது சட்ட பூர்வ உரிமைகளுக்கு பாதிப்பு ஏற்படாமல் நான் எந்த நேரத்திலும் விலகிக் கொள்ளலாம் என்பதை புரிகிறேன்.	
3)	எத்திக்ஸ் கமிட்டி மற்றும் ரெகுலேட்டரி அதாரிட்டீஸ்க்கும் நான் இந்த ஆய்விலிருந்து விலகினாலும் தற்போதைய மற்றும் எதிர்கால இந்த ஆய்வு சார்ந்த என் உடல்நல குறிப்புகளை என் அனுமதியின்றி பார்க்க முடியும் என நான் அறிகிறேன்.	
4)	இந்த ஆய்வில் கிடைக்கப்பெறும் குறிப்புகள் மற்றும் முடிவுகளை உபயோகப்படுத்த தடை செய்ய மாட்டேன் என சம்மதிக்கிறேன். ஆனால் அவைகள் விஞ்ஞானம் சம்மந்தப்பட்டவைகளுக்கு மட்டும் பயன் உள்ளதாக இருக்க வேண்டும்.	
5)	மேற்கூறிய ஆய்வில் பங்கேற்க நான் சம்மதிக்கிறேன்.	

ஆய்வில் பங்கேற்பவர் / சட்டபூர்வமாக
ஏற்கப்பட்ட நபர் கையொப்பம் அல்லது
பெருவிரல் பதிவு

சுய ஒப்புதல் படிவம்

கல்லீரல் மற்றும் கணைய அறுவை சிகிச்சையில் சின்பயோடிக் எனும் குடல்வழி மருந்தின் பயன்கள் மற்றும் விளைவுகள். இது ஒரு ஒரே முறையில் பயன்களையும், விளைவுகளையும் அறிந்து கொள்ள உதவும் ஆராய்ச்சி.

IMPACT OF PERIOPERATIVE SYNBIOTICS IN SURGERY FOR CHRONIC PANCREATITIS: A SINGLE BLIND PROSPECTIVE RANDOMIZED CONTROL TRIAL

ஆராய்ச்சி நிலையம் : அரசு ஸ்டான்லி மருத்துவமனை
சென்னை - 600 001.

பங்கு பெறும் நோயாளியின் பெயர் : வயது :

பங்கு பெறும் நோயாளியின் எண் : பாலினம் : ஆண் பெண்

நோயாளியின் விலாசம் :

நோயாளி இதனை (✓) குறிக்கவும்.

மேலே குறிப்பிடப்பட்டுள்ள மருத்துவ ஆய்வின் விவரங்கள் எனக்கு விளக்கப்பட்டது. என்னுடைய சந்தேகங்களை கேட்கவும். அதற்கான தகுந்த விளக்கங்களை பெறவும் வாய்ப்பளிக்கப்பட்டது.

நான் என்னை இவ்வாய்வில் தன்னிச்சையாகதான் பங்கேற்க அனுமதிக்கிறேன். எந்த காரணத்தினாலோ எந்த கட்டத்திலும் எந்த சட்ட சிக்கலுக்கும் உட்படாமல் என்னை இவ்வாய்வில் இருந்து விலக்கி கொள்ளலாம் என்றும் அறிந்து கொண்டேன். ☐

இந்த ஆய்வு சம்பந்தமாகவோ, இதை சார்ந்த மேலும் ஆய்வு மேற்கொள்ளும் போதும் இந்த ஆய்வில் பங்குபெறும் மருத்துவர் என்னுடைய மருத்துவ அறிக்கைகளை பார்ப்பதற்கு என் அனுமதி தேவையில்லை என அறிந்து கொள்கிறேன். என்னை ஆய்வில் இருந்து விலகிக் கொண்டாலும் இது பொருந்தும் என அறிகிறேன். ☐

இந்த ஆய்வின் மூலம் கிடைக்கும் தகவல்களையும், பரிசோதனை முடிவுகளையும் மற்றும் சிகிச்சை தொடர்பான தகவல்களையும் மருத்துவர் மேற்கொள்ளும் ஆய்வில் பயன்படுத்திக் கொள்ளவும் அதை பிரசுரிக்கவும் என் முழு மனதுடன் சம்மதிக்கிறேன். ☐

இந்த ஆய்வில் பங்கு கொள்ள ஒப்புக் கொள்கிறேன். எனக்கு கொடுக்கப்பட்ட அறிவுரைகளின்படி நடந்த கொள்வதுடன் இந்த ஆய்வை மேற்கொள்ளும் மருத்துவ அணிக்கு உண்மையுடன் இருப்பேன் என்று உறுதியளிக்கிறேன். என் உடல் பாதிக்கப்பட்டாலோ அல்லது எதிர்பாராத வழக்கத்திற்கு மாறான நோய்க்குறி தென்பட்டாலோ உடனே அதை மருத்துவ அணிக்கு தெரிவிப்பேன் என உறுதி அளிக்கிறேன். ☐

இந்த ஆய்வில் எனக்கு இரத்தம், சிறுநீர், எக்ஸ்ரே, ஸ்கேன் உட்பட அனைத்து பரிசோதனைகளையும் செய்து கொள்ள நான் முழு மனதுடன் சம்மதிக்கிறேன் ☐

பங்கேற்பவரின் கையொப்பம் ..... இடம் ..... தேதி

கட்டைவிரல் ரேகை (இந்த படிவம் படித்து காட்டப்பட்டு புரிந்து கைரேகை அளிக்கின்றேன்)

பங்கேற்பவரின் பெயர் மற்றும் விலாசம் .....

ஆய்வாளரின் கையொப்பம் ..... இடம் ..... தேதி

ஆய்வாளரின் பெயர் .....

MASTER CHART

S.No	Name	Age	Sex	Drug/	Organ	Diagnosis	Procedure	BMI	ASA	Intervention	operating time(min)	Blood loss(ml)	ICU stay	Passing	Hospital Stay	Antibiotics (days)	Patients with	Wound	Peritonitis	Pneumonia	UTI	Sepsis

				Placebo										(days)	stools Postop	(days)		infection					
1	Anitha	14	F	Drug	Pancreas	CCP	Frey Procedure	21.9	I	No	300	300	2	3	8		no					
2	Govindasamy	40	M	Placebo	Pancreas	CCP	Frey Procedure	25.3	I	No	300	300	5	4	9		no					
3	Ganesan	32	M	Drug	Pancreas	CCP	Frey Procedure	23	I	No	240	400	3	3	7		no					
4	Megalavathy	18	F	Placebo	Pancreas	CCP	Frey Procedure	24.2	I	No	300	250	4	4	10		no					
5	Srinivasan	40	M	Drug	Pancreas	CCP	Frey Procedure	23	I	No	300	400	4	4	12		no					
6	Janakiammal	55	F	Placebo	Pancreas	CCP	Frey Procedure	29	III	No	180	50	5	3	16	10	yes	yes				
7	Sivakumar	32	M	Placebo	Pancreas	CCP	Frey Procedure	21	I	Yes	240	250	4	3	16	7	yes	yes				
8	Manikandan	13	M	Drug	Pancreas	CCP	Frey Procedure	22	I	No	300	200	4	4	10		yes	yes				
9	Raja	18	M	Drug	Pancreas	CCP	Frey Procedure	18	I	No	360	600	8	3	20	3	yes			yes		
10	Sanasipandian	20	M	Drug	Pancreas	CCP	Frey Procedure	23	I	No	195	100	3	3	9		no					
11	Sekar	59	M	Drug	Pancreas	CCP	Frey Procedure	24	II	No	180	150	4	4	15	5	yes			Yes		
12	Shahjahan	37	M	Placebo	Pancreas	CCP	Inoperable															
13	Gnanprakasham	34	M	Placebo	Pancreas	CCP	Frey Procedure	29	I	No	420	600	6	3	16	7	yes	yes				
14	Radhakrishnan	50	M	Placebo	Pancreas	CCP	Frey Procedure	28	II	No	300	250	3	4	14	7	yes	yes				
15	Namachivayam	54	M	Placebo	Pancreas	CCP	Inoperable															
16	Anbalagi	45	F	Drug	Pancreas	CCP	Frey Procedure	28	I	No	240	350	5	4	12		no					
17	Devaraj	50	M	Placebo	Pancreas	CCP	Frey Procedure	27	II	No	240	350	4	4	14	7	yes	yes				
18	Vanmathy	18	F	Drug	Pancreas	CCP	Frey Procedure	23	I	No	240	150	5	4	13		no					
19	Marimuthu	51	M	Drug	Pancreas	CCP	Frey Procedure	23	II	yes	450	400	7	4	12		no					
20	Mohandas	66	M	Placebo	Pancreas	CCP	Frey Procedure	26	II	No	300	250	4	3	14	7	yes			yes		
21	Subamma	46	F	Placebo	Pancreas	CCP	Inoperable															
22	Suguna	62	F	Drug	Pancreas	CCP	Frey Procedure	24	II	No	330	350	5	6	17	3	yes	yes				
23	Kavitha	29	F	Drug	Pancreas	CCP	Frey Procedure	21	I	No	330	200	6	3	8		no					
24	Sekar	46	M	Drug	Pancreas	CCP	Frey Procedure	27	II	No	240	100	5	3	9		no					
25	Devadas	45	M	Placebo	Pancreas	CCP	Frey Procedure	24	I	No	450	500	7	3	16	7	yes			yes		
26	Krishnappa	45	M	Placebo	Pancreas	CCP	Frey Procedure	27	II	Yes	240	200	5	5	17	10	yes			yes		

27	Ravichandran	39	M	Drug	Pancreas	CCP	Frey Procedure	28	III	No	300	150	4	3	12		no								
28	Venkatesan	42	M	Placebo	Pancreas	CCP	Frey Procedure	24	I	No	300	250	6	4	13		no								
29	Kavitha	37	F	Placebo	Pancreas	CCP	Inoperable																		
30	Natrajan	70	M	Drug	Pancreas	CCP	Frey Procedure	18	III	no	420	500	5	3	12		no								
31	Guruswamy	68	M	Drug	Pancreas	CCP	Frey Procedure	17	II	no	360	100	3	4	9		no								
32	Chinnu	63	M	Drug	Pancreas	CCP	Frey Procedure	21	II	no	300	250	4	4	10		no								
33	Neela	47	F	Drug	Pancreas	CCP	Frey Procedure	29	I	No	300	250	4	4	10		no								
34	Pooja	17	F	Drug	Pancreas	CCP	Frey Procedure	18	I	No	300	200	4	3	16		no								
35	Babu	48	M	Drug	Panc eas	CCP	Frey Procedure	24	II	No	240	300	4	3	10		no								
36	Anjalai	55	F	Placebo	Pancreas	CCP	Frey Procedure	23	II	No	300	600	5	3	12		no								
37	Kavitha	35	F	Drug	Pancreas	CCP	Frey Procedure	26	II	No	270	100	4	3	10		no								
38	Bhuneshwari	19	F	Placebo	Pancreas	CCP	Frey Procedure	23	I	No	195	50	4	3	10		no								
39	Vidya	26	F	Drug	Pancreas	CCP	Frey Procedure	29	II	No	180	50	4	4	9		no								
40	Yogander	30	M	Drug	Pancreas	CCP	Frey Procedure	27	I	No	210	100	5	4	10		no								
41	Wilson	37	M	Placebo	Pancreas	CCP	Frey Procedure	21	I	No	240	100	4	3	10		no								
42	Leenas Joseph	53	M	Placebo	Pancreas	CCP	Frey Procedure	24	II	yes	360	460	8	9	21	14	yes								yes
43	Rahamathunisha	38	F	Drug	Pancreas	CCP	Frey Procedure	29	II	no	420	100	4	3	9		No								
44	Mahalakshmi	30	F	Drug	Pancreas	CCP	Frey Procedure	19	I	no	240	150	6	4	12		no								
45	Gnanammal	40	F	Drug	Pancreas	CCP	Frey Procedure	27	I	no	240	150	4	3	10		no								
46	Ayeshakani	32	F	Drug	Pancreas	CCP	Frey Procedure	29	I	no	300	200	6	3	8		no								
47	Ramachandran	51	M	Drug	Pancreas	CCP	Frey Procedure	32	II	no	495	750	4	2	6		No								
48	Kamali	13	F	Placebo	Pancreas	CCP	Frey Procedure	18	I	no	120	150	3	2	14	7	yes							yes	
49	Jamila	70	F	Placebo	Pancreas	CCP	Frey Procedure	27	II	no	300	200	3	2	12		no								
50	Ramaswamy	57	M	Placebo	Pancreas	CCP	Frey Procedure	23	II	no	240	200	4	3	7		no								
51	Ramachandran	43	M	Drug	Pancreas	CCP	Frey Procedure	24	I	no	270	100	4	3	10		no								
52	Krishnachandranahar	42	M	Drug	Pancreas	CCP	Frey Procedure	27	II	no	135	150	4	4	9		no								

53	Michael	68	M	Drug	Pancreas	CCP	Frey Procedure	23	II	no	180	200	4	3	10		no						
54	Jayanthi	40	F	Placebo	Pancreas	CCP	Frey Procedure	21	I	no	180	50	6	4	10	16	yes			yes			
55	Ellaiyammal	45	F	Drug	Pancreas	CCP	Frey Procedure	24	II	no	300	1000	9	4	9		no						
56	Vijayakumar	31	M	Placebo	Pancreas	CCP	Frey Procedure	26	I	no	240	60	4	3	11		no						
57	Ponnuvelu	40	M	Drug	Pancreas	CCP	Frey Procedure	23	II	no	240	75	4	4	10		no						
58	Periyanayagam	55	M	Placebo	Pancreas	CCP	Frey Procedure	19	II	no	300	100	5	7	14	10	yes				yes		
59	Suresh	32	M	Placebo	Pancreas	CCP	Frey Procedure	24	I	no	300	100	4	4	16		no						
60	Rajaram	42	M	Drug	Pancreas	CCP	Frey Procedure	28	I	no	300	50	3	3	10		no						
61	Vasanthi	46	F	Placebo	Pancreas	CCP	Frey Procedure	24	II	no	360	600	4	4	9		no						
62	Murali	37	M	Placebo	Pancreas	CCP	Frey Procedure	31	I	no	240	500	7	2	12		no						
63	Radhakrishnan	66	M	Drug	Pancreas	CCP	Frey Procedure	23	II	no	240	200	4	4	9		no						
64	Parivallal	18	M	Drug	Pancreas	CCP	Frey Procedure	17	I	no	210	200	6	3	9		no						
65	Babyammal	37	F	Drug	Pancreas	CCP	Frey Procedure	18	I	no	240	250	4	4	14	5	yes				yes		
66	Vimala	21	F	Placebo	Pancreas	CCP	Frey Procedure	23	I	no	300	150	7	3	10		no						
67	Santhosh	31	M	Placebo	Pancreas	CCP	Frey Procedure	21	II	no	330	300	4	2	10		no						
68	Velumudali	48	M	Placebo	Pancreas	CCP	Frey Procedure	26	I	no	240	100	6	3	10		no						
69	Bhanumathi	67	F	Placebo	Pancreas	CCP	Frey Procedure	18	II	no	240	200	4	4	8		no						
70	Jebagnanam	58	M	Placebo	Pancreas	CCP	Frey Procedure	34	II	no	420	200	7	2	16	10	yes			yes			
71	Vijayakumar	31	M	Drug	Pancreas	CCP	Frey Procedure	23	I	no	300	100	4	6	10		no						
72	Chokkalingam	56	M	Placebo	Pancreas	CCP	Frey Procedure	25	II	no	300	200	4	2	9		no						
73	Gunavathy	21	F	Placebo	Pancreas	CCP	Frey Procedure	18	I	no	300	150	4	2	10		no						
74	Rajendran	48	M	Placebo	Pancreas	CCP	Frey Procedure	24	II	no	240	100	4	5	7		no						
75	Bharathi	37	M	Drug	Pancreas	CCP	Frey Procedure	21	I	no	240	60	6	4	10		no						
76	Uma	45	F	Placebo	Pancreas	CCP	Frey Procedure	22	I	no	300	160	6	3	19	10	yes				yes		
77	Rose Reddy	64	M	Placebo	Pancreas	CCP	Frey Procedure	24	II	no	300	150	5	5	10		no						
78	Kaveri	24	F	Placebo	Pancreas	CCP	Frey Procedure	28	I	no	240	100	4	4	6		no						

79	Asmath	16	F	Placebo	Pancreas	CCP	Frey Procedure	19	I	no	240	50	4	3	10		no							

Cholangitis	Empyema	Others	Bacteria grown	Hb preop	Hb POD 1	Hb POD 5	Hb POD 10	TC Preop	TC POD1	TC POD 5	TC POD 10	Bilirubin Preop	Bilirubin POD 1	Bilirubin POD 5	Bilirubin POD 10	Albumin Preop	Albumin POD 1	Albumin POD 5	Albumin POD 10	BUN preop	BUN POD 1	BUN POD 5	BUN POD 10
				10.3	10.7	9.8	10.1	8200	11000	5300	6700	0.41	1	0.7	0.6	3.8	3.9	4.7	4.1	13.23	15	14	18
				14.1	15.7	13.1	14.5	7000	9700	5900	4600	0.59	0.4	0.6	0.6	3.7	3.3	3.5	3.7	28	17	18	15
				11.6	12.1	11.3	11	13000	15000	13200	11000	0.14	0.21	0.8	0.5	5	4.1	4.2	4.1	14.01	21.1	19.1	19.2
				10.5	9.1	9	9.8	4500	8900	8500	6500	0.5	0.7	0.6	0.6	3.3	2.9	3.1	3.1	13	14	16	15
				10.6	10.7	10.6	10.6	7800	10400	8900	8300	0.91	0.8	0.7	0.7	3.5	3.1	3.3	3.4	17	13	15	18
			E.Coli- TA	11	12.5	8.7	9.8	5200	12100	8900	7800	0.31	0.8	0.8	0.7	3.8	3	3	3.1	27	35	35	28
			Kleb-Imip, Erta	9.8	8.9	10.1	10.1	12100	13000	10100	9400	1.1	0.9	0.7	0.8	2.9	2.6	3.1	3.2	32.1	14.1	12.3	15.1
			Kleb-Imip, Erta	9.1	8.9	9.1	9.3	4500	8900	7800	8700	0.7	0.5	0.6	0.5	4.5	3.8	4	4.2	14	12.1	14	15
			E.Coli- TA	10.2	7.8	8.9	10.1	6800	14000	15000	9800	0.6	1.1	0.9	0.7	3.8	2.9	3.1	3.2	26	19	12.1	14.1
				11	10.8	11.2	11	4500	10200	9600	5400	0.8	0.6	0.5	0.6	4.6	3	3.5	3.7	28	33	18	15
			Kleb-Imip, Erta	13.2	12.9	12.2	12.6	12900	14500	8900	7800	0.6	0.5	0.4	0.7	3.6	3.1	3.2	3.1	14.1	23	21.5	24.3
			E.Coli- TA	9.9	8.4	8	9.1	10800	14500	7900	6800	2.68	2.7	1.8	1.4	3	3	3	2.1	47.7	50	48.1	49.56
			CONS-Ampi, Cip, Van	10.3	9.7	9.1	9.2	5500	7600	9800	8800	3.7	3.1	2.1	1.8	3.3	3.1	3.3	3.3	10.37	18.1	13.1	19.2
				10.5	10.9	9.8	9.8	6500	11000	12500	8900	0.7	0.9	0.9	0.7	3.9	3.2	3.4	3.5	18	21	19	21
			CONS-Ampi, Cip, Van	10.7	9.8	9.1	10.1	4500	6500	5600	7600	0.6	0.5	0.4	0.6	3.6	3.1	3.1	3.1	14.1	23	22	23
				11.6	10.9	10.9	11.1	6500	8900	7800	7800	0.26	0.31	0.52	0.71	3.8	3.2	3.7	3.8	10.8	12	14	12.1
				11.9	15.5	10	9.1	6300	12100	4900	5600	2.6	0.7	0.8	0.7	4.4	3.2	2.9	3.2	25.44	53	24	20
			Acinetobacter - Imi	10.5	9.1	9	9.8	4500	8900	13500	9900	0.5	0.7	0.6	0.6	3.3	2.9	3.1	3.1	13	14	16	15
			E.Coli- TA	11	11.1	8.7	9.9	5200	12000	8900	7800	0.41	0.8	0.8	0.7	3.8	3	3	3.1	27	35	21	28
				11.4	13	11.5	12.1	7500	14500	10000	9700	0.58	0.6	0.7	0.6	4	3.7	4	4	27.35	25	18	15
				11.8	12.5	11.7	11.9	6700	11000	9800	6800	0.7	0.5	0.7	0.7	4.2	3.7	3.5	3.6	16.57	18	19.1	18.4
			Kleb-Imip, Erta	13.3	12.1	11.4	12.1	6200	7800	7600	8700	7.6	12.1	6.1	1.1	3.6	3.1	3.1	3.3	21.1	15	20.1	18
			MRSA-Imi	13.7	12.8	10.1	9.1	9600	10400	12000	12500	0.41	0.61	0.8	0.8	3.6	3.2	3.3	3.2	20.52	19	19.1	21
				10	10.1	11.1	10.9	14000	12100	10000	9900	0.94	0.78	0.45	0.31	3.1	3	3.1	3	13.69	12.1	17.1	12.1
				11.1	10.9	10.4	11.1	6500	6800	7500	7800	0.26	0.31	0.52	0.71	3.8	3.2	3.5	3.8	10.8	12	13.1	12.1
				11.3	12	10.8	10.1	11800	12000	9800	9100	6.3	7.5	4.1	2.1	3.6	3.1	3.6	3.5	18	28	14	19
				13.6	12.9	13.1	12.8	11300	8900	8800	6600	1.72	1.4	1.5	0.9	2.9	2.8	3.1	3	20.85	22.1	24.9	20.1
				11.4	10.3	10.8	10.8	10200	9800	9100	8800	1.92	1.9	1.4	0.9	3.2	3.1	3.3	3.1	15.6	14.1	15.5	19.4
				10.8	9.2	10.3	10.2	4700	6800	7500	8500	0.71	0.5	0.6	0.4	4.4	4.2	4.3	4.2	23.47	21.9	23.1	21.9
				9.5	9.1	9.9	10.1	7700	6700	4500	8900	0.38	0.4	0.5	0.6	3.3	3.1	3.3	3.2	14.48	13.9	10.1	12.9

				12.2	11.9	11.9	12.1	13300	14100	10000	9800	2.9	3.5	1.8	1	3	3.1	2.9	3	6.32	19.2	12.3	14.2
				8	3.8	10.2	9.8	9400	9200	8000	9300	13	9.7	13.8	10.1	2.9	1.8	2.8	3.3	27	30	36	28
				11.5	11.4	11.3	10.9	8600	8300	8000	9100	0.85	0.9	0.5	0.4	4.1	3.9	4.1	4	11.52	29.1	23.1	18.1
				12.2	11.8	10.5	10.3	11800	15400	13400	8100	0.32	0.33	0.51	0.54	4.7	4.5	4.3	4.1	16.88	12.1	14	11.1
				13.4	12.9	12.3	12.9	8700	8400	8900	8400	0.64	0.41	0.56	0.31	4.5	4.1	4.4	4.1	17.7	14.1	19.1	12.1
				12.1	12.9	12.3	12.3	4500	6700	4100	4300	1.1	1.1	1.2	1	4.5	3.8	4.1	4	17.57	18.2	12.1	21.2
				10.3	10.4	9.8	10.1	8200	11000	5500	6700	0.41	1.1	0.7	0.6	3.8	3.9	4.7	4.1	13.23	15	14.1	18
			E.Coli-T, A	11.6	10.8	10.8	10.3	5200	6500	6300	4500	0.81	2.1	4.6	4.1	3.9	3.6	3.4	3.1	28.31	24.1	23.1	19.1
				8.3	8.6	11	10.7	10700	19200	7400	8600	0.76	0.9	0.7	8	4.3	3.2	2.8	3.4	16.06	32.02	31	28
				10.6	10.4	10.3	10.2	8600	6500	5600	4500	0.7	0.7	0.32	0.87	5.3	4.9	4.7	4.8	28	21.1	23.1	19.1
				10	9.8	9.9	10.2	12100	6800	8600	4600	0.72	0.71	0.64	0.55	4.6	4.1	4	4.1	27.84	22.4	23.1	16.9
				10.3	10.2	10.2	10.4	10200	7600	7400	8400	0.56	0.8	0.65	0.56	2.9	3	3.1	3	25.45	25.4	23.1	22.9
				14.7	10	8.1	9.8	9900	10700	7700	6500	26.6	25.7	20.5	10.1	3.6	3.3	2.1	3.4	50.4	35	128	87
			E.Coli-T, A	11	10.1	10.8	10.7	15800	20600	14000	6400	0.38	0.4	0.4	0.5	4.5	4.1	3.8	3.8	20.29	18.7	12.1	21.1
				13.2	12.3	13.2	12.9	6800	7800	8700	4300	2.07	1.8	1.8	1.4	4.4	4	3.8	3.8	28.6	24.1	21.2	24.1
				7.8	6.6	7.8	8.3	5100	8400	7900	8600	0.98	0.85	0.91	0.24	3.9	3.4	3.3	3.4	21.68	26	24.1	28.1
				11.7	10.2	10.4	10.9	11200	10200	9800	8900	0.39	0.56	0.64	0.76	3.6	3.5	3.4	3.7	12.2	14.9	21.2	20.8
				12.1	12	11.8	11.1	5000	7600	6700	4600	0.6	0.58	0.64	0.67	3.5	3.4	3.1	3.8	18.57	19.8	18.2	13.1
				12.4	12.1	12.2	10.2	6300	7700	6400	6500	8.2	8.1	4.3	3.1	4	3.8	3.9	3.8	22.49	21.4	21.9	22.1
			Kleb-Imip, Erta	5.7	8.4	9.1	9.1	5400	4500	6400	8800	0.34	0.23	0.5	0.41	2.7	2.7	2.8	2.8	15.83	19.1	18.1	18.5
				12.6	8.3	9.3	10.1	6300	7700	8700	9300	0.8	19.1	18.1	6.7	4.4	2.4	2.7	3.1	29	38	32	29.1
				12.5	10.2	11.2	11.2	7000	8100	8400	6000	0.36	0.35	0.65	0.43	4.2	4.1	4.1	4	13	14.1	16.3	10.1
				11.4	11.4	12.1	11.3	6400	7900	8400	6700	0.8	0.45	0.59	0.65	3.9	3.7	3.5	3.5	23	18.2	17.1	21.2
			Kleb-Imip, Erta	11.5	11.2	10.9	11.1	6000	6700	8600	6600	0.6	0.96	0.54	0.55	3	3.1	3.3	3.4	29.1	24.1	24.5	29.3
				12.3	13.6	13.1	13.3	13800	29400	13800	11000	0.7	0.5	0.7	0.6	4.1	3.6	3.5	3.7	27.66	24.76	19.87	19.81
				13.7	13.1	13.3	13.3	9000	11000	9200	10000	1.3	0.9	0.5	0.6	4.6	4.1	4.1	4	19.92	18.1	21.1	23.1
				8.8	9.1	9	8.7	15900	14000	11800	10300	0.94	0.54	0.98	0.54	2	1.9	2.1	2.2	19.28	29.1	25.6	23.4
				11.1	11	8.9	10.6	7600	6600	9600	8400	13.8	14.1	7.6	3.1	4	3.6	3.5	2.9	31.3	22	23	21.2
				12.9	12.3	12.1	11.9	6800	8700	8300	8700	12.9	11	8.1	4.3	3.9	3.8	3.6	3.8	21.69	29.4	28.3	24.8
				15.7	14.1	14.6	14.8	7900	11000	8900	8700	0.41	0.6	0.71	0.31	4	3.8	3.7	3.8	13.28	14.1	13.8	13.2
			Kleb-Imip, Erta	10.5	10.1	9.8	9.9	7300	8400	8500	8300	2.4	2.1	1.9	1.2	2.7	2.1	2.9	2.9	18.28	19.2	18	14.2
				9.7	9.2	9.4	9.4	7500	7600	7800	7400	0.7	0.9	0.8	0.3	5.1	4.6	4.9	4.8	15	19.2	10.3	9.1
				10.3	10.2	10.3	10.2	4200	4000	4100	4400	0.23	0.3	0.4	0.5	3	2.9	2.9	2.9	24.04	28	24.1	23.1
				10.1	9.8	9.2	9.8	4500	6500	5500	7600	0.6	0.5	0.5	0.6	3.6	3.1	3.1	3.1	14.1	23	21	23
				13.7	13.6	12.9	12.8	8400	7700	7400	6700	0.42	0.4	0.8	0.6	4.1	3.8	3.8	3.5	25.11	24.1	29.4	28.4
			Kleb-Imip, Erta	12.7	8.3	10	12.1	8800	9600	10300	9800	23.9	16	20.7	15.1	3.8	2.1	3	3.2	28.96	36	30	23.1
				13.2	13.1	12.4	13	6500	6700	7600	8400	2.93	2.1	1.1	1.3	3.4	3.3	3.4	3.1	15.69	18.1	13	19.4

				10.5	9.4	10.1	10.2	7100	10200	9800	8100	0.98	0.8	0.8	0.3	3.6	3.6	3.5	3.6	15.87	17.3	16.3	19.2
				12.1	11.3	10.3	11.1	7200	8900	10100	8900	0.77	0.84	0.49	0.55	4.1	3.7	3.6	3.6	21.09	18.4	19.4	21.4
				8.5	9.1	8.8	9.8	5900	7600	7800	6400	0.32	0.39	0.39	0.91	3	2.8	2.9	3.1	24.17	23.7	24.3	21.4
				10.9	10.5	10.3	10.4	7100	7000	4700	6100	1.43	1.1	1.4	0.98	3.8	3.4	3.1	3.4	22	23.1	23.1	18.1
				10.7	9.8	9.1	10.1	4500	6500	5400	7600	0.6	0.5	0.3	0.6	3.6	3.1	3	3.1	14.1	23	18	23
				12.1	11.4	12.1	11.9	7700	7800	5700	7400	0.44	0.45	0.43	0.43	3.7	3.2	3.1	3.4	15.1	16.3	13.9	14.2
				12	11.1	11.3	11.2	6800	6500	6500	5500	0.7	0.94	0.81	0.32	3.7	3.5	3.7	3.6	32	18.3	16.4	18.9
				11.3	10.4	10.2	10.4	6400	6600	5600	8600	0.36	0.54	0.54	0.49	3.8	3.5	3.6	3.6	21.89	22.4	21.9	19.8